TRANSACTIONS

OF

The Association of Life Insurance Medical Directors of America

SIXTY-FOURTH ANNUAL MEETING

James R. Gudger, M. D.
Editor

VOL. XXXIX

PRESS OF
Recording & Statistical Corporation
New York City
1956

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Printed in U. S. A.

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Transactions of The Association of Life Insurance Medical Directors of America

SIXTY-FOURTH ANNUAL MEETING

The Sixty-fourth Annual Meeting of The Association of Life Insurance Medical Directors of America convened on Wednesday morning, October 19, 1955, in the Keystone Room of the Hotel Statler, New York, N. Y., at eleven-ten o'clock, Dr. Richard L. Willis, President of the Association, presiding.

PRESIDENT RICHARD L. WILLIS — The meeting is called to order, gentlemen. It is a great pleasure to me to welcome the Chairman of the Medical Section of the American Life Convention, and to invite him to address us at this time. Dr. Norman B. Cole, will you please come forward.

DR. NORMAN B. COLE — Thank you for the courtesy, Dr. Willis. It is a real pleasure and an honor for me to bring to you, Dr. Willis, and your group, the warm greetings of the Medical Section.

The Medical Section meets next June — on Monday, Tuesday and Wednesday, June 18, 19 and 20 — at White Sulphur Springs. Dr. Joseph Travenick is our Program Chairman this year, and I want to tell you that he has his program practically completed now. It is going to be a good one. There is just one thing I will say about it. There is one item in his program that is labeled, "Do not open until June 20th." Now, you can figure out what that is going to be.

We welcome you, Dr. Willis, and your group there, and we hope you will all come. We will have plenty of tennis balls and golf balls, and we have ordered good weather and we are going to have a good time. Thank you.

DR. WILLIS — Thank you, Dr. Cole.

We are glad to have with us Dr. Francis R. Dieuaide, Scientific Director of the Life Insurance Research Fund. He needs no introduction to this group and we will now hear his discussion of the work being carried on by the Fund.

DR. FRANCIS R. DIEUAIDE — The Life Insurance Medical Research Fund now has 143 member companies, representing over 90 per cent of life insurance in force in the United States. Contributions to the Fund for 1954-55 total approximately $960,000. The year's awards amount to $929,400, including 66 grants in aid of cardiovascular research programs and 27 fellowships for training in cardiovascular research.

Among the results of recent research, those bearing on arteriosclerosis and coronary disease are of special and timely interest. Attention has been newly directed to the possibility that repeated focal injuries to the arteries may play a key role in preparing the tissue for the development of arteriosclerosis. Injuries of a general basic nature such as those caused by various infections (and also by hypertension) are in question. It has been shown that following experimentally produced arterial damage, elevation of blood lipoproteins causes lesions resembling human arteriosclerosis in the damaged areas.

An important finding is the discovery of a parallelism in three animal species between their susceptibility to arteriosclerosis and their ability to synthesize certain phospholipids closely related to lecithin. Susceptibility to arteriosclerosis, so marked in man, varies greatly in animals. An explanation will be a long step forward.

Work on cholesterol metabolism has continued to be productive. Absorbed dietary cholesterol has been shown to travel mainly in the lymphatics in particulate form. The reticulo-endothelial system has been found to play a central role in the removal of such cholesterol from circulation. The interconversions of cholesterol-carrying molecules from one form to another has been studied in the blood. Our knowledge of cholesterol synthesis in the body has been further increased, the work now having advanced to the study of the enzyme systems concerned. Several methods of regulating cholesterol synthesis have been discovered, the most important being perhaps through the action of sex hormones.

It has been shown that arteriosclerotic lesions in animals are in part at least reversible. As you know, arteriosclerosis is not

considered to be a necessary part of old age. It is encouraging to know that the disease is neither inevitable nor immutable.

One of the investigators aided by the Fund has made progress in the development of a surgical method for the revascularization of the myocardium in coronary artery disease.

Current basic work on hypertension largely concerns the actions of adrenal hormones and sympathetic nerves. New help in the evaluation of hypertensive cases has been provided by the development of an objective method for assessing degenerative changes in the retinal arteries. Impairment of retinal artery reactivity has been shown to occur as a rule before alterations in kidney function. Much work has been done with the relatively new anti-hypertensive agents, such as the hexamethonium compounds and rauwolfia. These drugs are helpful in certain cases, but they apparently have many limitations.

In an important contribution to the use of commissurotomy for mitral stenosis, it has been shown that patients in whom heart muscle failure predominates, rather than valvular obstruction, do not benefit from the operation.

One of the Fund's Fellows during the past two years has largely contributed to the successful surgical use of the cross-circulation method. As you know, in this method a relative's or friend's heart and lungs perform the functions of those of the patient who is being operated on. The new procedure is expected to enable surgeons to do many heart operations hitherto impracticable.

A survey of current activities of the first 100 Fund Fellows (awards before June 1950) has shown that some 60 are in full-time positions concerned with teaching and research, 29 having attained the rank of assistant professor or better. It is not to be expected that such a high percentage of former Fellows will ultimately remain in this type of work. The result to date, however, is extremely gratifying.

This fall the Fund reaches its tenth anniversary. Our net awards for the ten years total $7,209,103. Administrative expenses total $480,825. In no year have they exceeded 7 per cent of contributions. In all, 247 research programs and 302 fellowships have been supported. Research has been aided in 110 insti-

tutions widely distributed in the United States and Canada.

Our new Annual Report, now being mailed to all of you, contains a review of the major research aided by the Fund. We hope you will find time to read this section which occupies the first twenty pages of the Report.

During the recent sessions of the American Life Convention, executive officers of Fund member companies attended an anniversary luncheon at which Dr. Alan Gregg, Vice President of The Rockefeller Foundation, addressed the gathering. In the course of his talk, Dr. Gregg said: "You were the first group to concentrate attention and support to research and training fellowships in the field of cardiovascular disease. Such concentration gives you, as your annual reports prove, a knowledge second to none of where to find the best minds and spirits in this field. That is a real accomplishment and a priceless present asset, because by concentration on one area you have the time as well as the obligation to learn the most significant problems of cardiovascular disease and the most promising leads to follow or explore. The competence of your staff and its Advisory Council keeps the cost of making your grants effectively at an extremely low level. In so doing you have provided a fine standard for other agencies who have supplemented your work, as well as followed your example. Furthermore, as you may or may not be aware, your sponsorship is known and highly prized by medical investigators and sought after in growing measure."

I wish to take this opportunity to express my deep appreciation of the invaluable help and support generously given by all who have served with the Fund as Medical Directors' Representatives, as well as for the opportunity to make this report to you.

PRESIDENT WILLIS — Thank you, Dr. Dieuaide.

T-wave changes in electrocardiograms is a subject about which we have never known enough. A paper has been prepared by Dr. Charles E. Kiessling, Associate Medical Director, Dr. Royal S. Schaaf, Assistant Medical Director, and Miss Annie Mary Lyle, Senior Underwriting Research Analyst and Fellow of the Society of Actuaries, all of The Prudential Insurance Company. Dr. Kiessling will present the paper, the subject of which is, "Mortality Studies of Isolated Electrocardiographic T-Wave Changes."

MORTALITY STUDIES OF ISOLATED ELECTROCARDIOGRAPHIC T-WAVE CHANGES

CHARLES E. KIESSLING, M. D., *Associate Medical Director*
ROYAL S. SCHAAF, M. D., *Assistant Medical Director*
ANNIE MARY LYLE, F.S.A., *Senior Underwriting Research Analyst*

The Prudential Insurance Company of America
Newark, New Jersey

We are frequently confronted with the problem of evaluating questionable or abnormal T-wave changes in electrocardiograms from applicants without other impairments. Those with enough courage to impose a higher premium rating because of such T waves, and especially if the T-wave changes are slight, expect a protest soon from the applicant or sales representative implying gross error or gross ignorance on the part of the underwriter.

Clinicians are apt to minimize the importance of questionable T waves in tracings from otherwise normal individuals, and we think their action is justifiable from a clinical standpoint. After all, the clinician can continue to observe his patient, re-examine him at some future date and, if necessary, change his previous opinion. As underwriters, however, we must make an irrevocable decision and must speak with the voice of a prophet for all time. The evaluation of an electrocardiogram made on a life insurance applicant and the evaluation of an electrocardiogram made on a patient are processes that differ considerably. Clinically, one might wish to give a patient assurance but might not care to offer the same person life insurance. One would be willing to "say it" but perhaps not to "pay it."

As we all know, numerous conditions both pathological and physiological, cardiac as well as non-cardiac, can cause alteration of T waves. In some instances abnormal T waves are evidence of cardiac disease, perhaps of latent type, but in other instances they are not. We know we cannot separate the normal hearts from the impaired hearts by means of the electrocardiogram alone.

However, there is no reason why we cannot look at the problem objectively and grade and group our T-wave abnormalities just as we do any other abnormal sign or symptom. We can then rate the groups appropriately and collect the extra premiums from those that show an increased mortality. But to do this we must have an approximate idea what that increased mortality is.

The material on which this study was based comes from a file containing about 22,000 electrocardiograms on about 10,000 Prudential Insurance Company of America employees. This file is perhaps unique. Miss Annie Mary Lyle originated it and has supervised its development through the years since 1933. It has now reached an age and such proportions that it is beginning to give us tentative answers to our electrocardiographic problems.

Since the source of the material might be pertinent and influence any appraisal of the results of this study, the records and file are described briefly. This file includes not only a copy of every electrocardiogram made in the Home Office since 1933 but it also includes all pertinent medical data collected on that individual. Each electrocardiographic examination is mounted on an 8 by 10 inch card. On the reverse side of the card are the identifying data together with the age, weight and height. Here, also, are recorded the clinical information, laboratory findings, x-ray reports and electrocardiographic interpretation. Across the top of the card appear various colored tabs pertaining to different conditions in specified columns indexing the electrocardiographic and clinical data.

We estimate that within the age groups covered (40 to 69 years) in this study, 60 per cent of the file is composed of data on individuals who are normal clinically and 40 per cent is on individuals who have some evidence of cardiovascular disease, usually of hypertensive or arteriosclerotic type. This is mentioned only as a matter of interest since, as you will see, material was selected only from clinically normal individuals for this investigation.

The study began with a systematic search of the file for individuals whose tracings showed only T-wave changes and whose examinations, clinical and otherwise, were negative, hence the title "Mortality Studies of Isolated Electrocardiographic T-wave

Changes." The material was further restricted to include only males between the ages of 40 and 69 years, among whom coronary disease is considered to be most prevalent. The entire file was surveyed, each mounted tracing examined and those cases assembled which showed abnormal or questionable T-wave changes. When a card was found which fulfilled the electrocardiographic requirements, the clinical data was reviewed. If there were no adverse clinical data, that individual was included in the study. Finally, the individuals chosen were followed up to June 30, 1955. No new entrants were added after December 31, 1954, so our follow-up period ranges from six months to 22 years, averaging six to seven years.

The tracings finally selected were arbitrarily divided into two groups, one showing slight T-wave changes which, for want of a better term, were called minor T-wave changes and another showing marked, or major, T-wave changes. These two groups comprise the material on which this presentation is based.

Two additional groups were then selected: one composed of individuals who were normal clinically and who had normal electrocardiograms, and another composed of individuals who had had a coronary occlusion but no associated disease or hypertension. These two groups were designed to serve as controls or a frame of reference for our investigation of those showing T-wave changes.

We then have four groups: one showing minor T-wave changes, another showing major T-wave changes, and these two bracketed by the normal persons on one hand and those with the history of a coronary episode on the other. Each group will be described separately.

The normal group is comprised of individuals who had normal electrocardiograms and who appeared normal clinically. Some of them had symptoms which were not considered significant. They had no evidence of organic disease, cardiac or otherwise. Those with faint systolic murmurs, considered by the examining physicians to be physiological, were included among the normal people. Blood pressure readings were consistently below 150/90 in all cases. Some had arrythmia of a few ectopic beats. A family history of cardiovascular disease was disregarded. These indi-

viduals, all males, were between the ages of 40 and 69 at the time they were included in the study.

Table 1

Analysis by Groups

Group	Total Number	Deaths	Per Cent Actual to Expected Deaths	Per Cent Deaths from Cardiovascular Causes	Per Cent Total Number Subsequently Developing Coronary Occlusion
Normal	1,388	75	84	47	3.2

There were 1,388 in the normal group. Over an average period of observation of six to seven years, 3.2 per cent developed a subsequent coronary occlusion. Seventy-five died, producing a mortality ratio of 84 per cent, computed by the 1946 to 1949 Basic Table, Select and Ultimate. Of those who died, cardiovascular disease was the cause in 47 per cent. These figures are considered to be reliable and conform to the expected in a group of this type.

Contrasted with the normal, and presented merely to serve as a basis for comparison with our abnormal T-wave group, the following observations were made on the group that had coronary disease. There were 112 individuals who had a coronary occlusion and survived the acute episode by at least 60 days, and whose disease was uncomplicated by diabetes, valvular disease of the heart or any other organic impairment. Some of them had arterial hypertension prior to the occlusion but their blood pressure was

Table 2

Analysis by Groups

Group	Total Number	Deaths	Per Cent Actual to Expected Deaths	Per Cent Deaths from Cardiovascular Causes	Per Cent Total Number Subsequently Developing Coronary Occlusion
Normal	1,388	75	84	47	3.2
Previous coronary history	112	40	526	95	—

normal following the occlusion. Forty deaths among them produced a mortality ratio of 526 per cent. Of these 40 persons 95 per cent died of cardiovascular disease. This mortality, 526 per cent, may seem somewhat high, but it was computed immediately after recovery from the coronary occlusion. Persons surviving coronary occlusion and who have been well for several years experience a slightly lower mortality, but for our purposes the figure 526 per cent will suffice.

The two groups of individuals on whom the investigation was conducted, one showing marked or major T-wave changes and the other slight or minor T-wave abnormalities, are now compared with the previously described normal and coronary history groups.

Major T-wave changes are those classified as grossly abnormal. They consist of T waves that are definitely diphasic or inverted where one normally would expect an upright T wave, such as in leads I, II, and also the left precordial leads. This applies to aV_L and aV_F in those tracings where the QRS complexes are tall and mainly upright. The abnormal T wave might be present in only one lead, in several leads, or any combination of leads. The electrocardiograms shown in figures 1 through 6 are representative of those comprising this group.

Leads I, II, III and the unipolar extremity leads, aV_R, aV_L and aV_F, appear across the top of the figure in this order. The bottom row contains the precordial leads V_1 through V_6.

We searched the file for electrocardiograms such as these, but included in the study only those from persons whose clinical examinations and case histories were negative. Individuals with hypertension, organic murmurs or diabetes, and even those with irrelevant disease, such as peptic ulcer, tuberculosis or nephritis, were excluded. Physiological murmurs were included. A few showed scattered ectopic beats. In some cases the T-wave changes persisted for a long time or appeared in several records. In other cases the changes were evanescent. We made no attempt to subdivide the group from this point of view.

It is significant to note that only 43 persons could be found among our male employees between the ages of 40 and 69 who had electrocardiograms showing these changes and who were

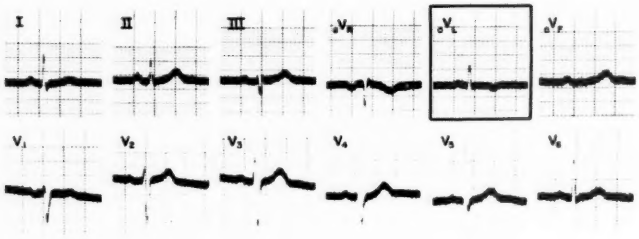

Figure 1

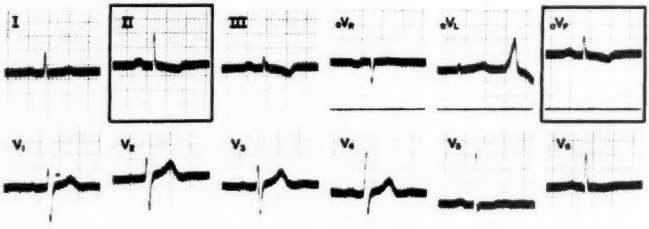

Figure 2

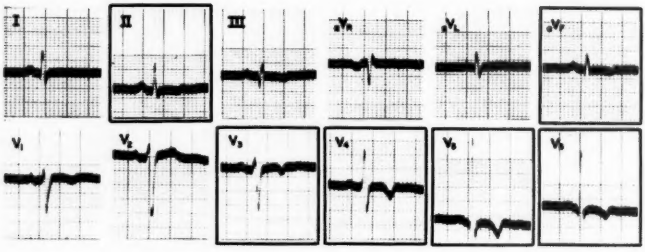

Figure 3

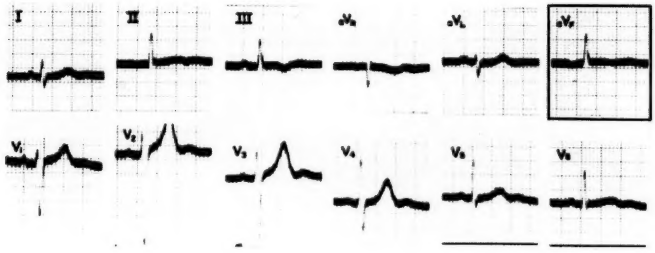

Figure 4

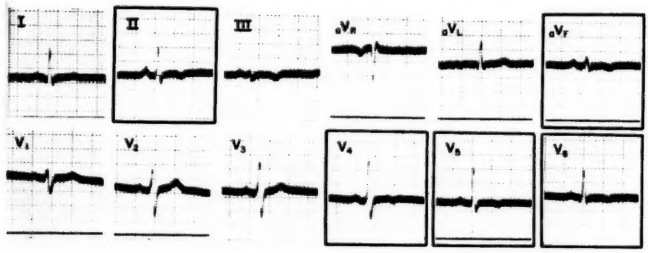

Figure 5

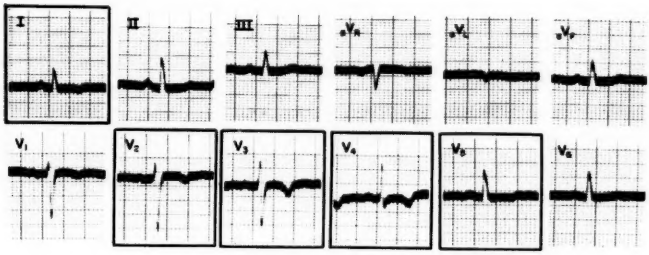

Figure 6

normal clinically. The file contains numerous electrocardiograms showing similar abnormalities, but individuals having such records usually had other evidence of cardiovascular disease, such as hypertension, a preceding coronary occlusion, angina or a valvular defect. When there is a tracing showing such T-wave changes and there is apparently no other evidence of cardiovascular disease, one is justified in being suspicious of not getting a complete clinical picture. Isolated changes of this type are possible but they are very unusual.

The 43 cases of major T-wave changes had seven deaths among them with a mortality ratio of 302 per cent. Sixteen and three tenths per cent of the group subsequently developed a coronary occlusion over an average observation period of 5.4 years. So, this is evidence of what to expect from T-wave changes such as these, even though there were no clinical abnormalities. Among the 7 deaths, 71.4 per cent were the result of cardiovascular disease.

Table 3

Analysis by Groups

Group	Total Number	Deaths	Per Cent Actual to Expected Deaths	Per Cent Deaths from Cardiovascular Causes	Per Cent Total Number Subsequently Developing Coronary Occlusion
Normal	1,388	75	84	47	3.2
Major T-wave changes	43	7	302	71.4	16.3
Previous coronary history	112	40	526	95	—

We had an additional 19 cases that showed major T-wave changes in the tracing and appeared normal clinically except that they had a history of chest pain suspected of being angina pectoris. Since applicants sometimes forget to mention a history of suspicious chest pain, it was interesting to see what effect on mortality the inclusion of such cases might produce. The mortality was recomputed after adding these 19 cases to the original 43,

and a mortality ratio of 335 per cent was obtained. One may conclude that a fair proportion of individuals who have abnormal electrocardiograms, such as these, also have angina pectoris, whether they admit it or not. In this instance, among a total of 62 cases showing isolated, grossly abnormal T waves, 19, or almost one-third, had chest pain which may have been angina.

The group showing slight or minor T-wave changes was more interesting, since these changes are more frequently encountered as isolated findings. They represent more of a problem than the group with grossly abnormal T waves just presented.

The T waves in this group were characterized by their disproportionately low amplitude, as illustrated in figures 7 to 12. However, those with low T waves in lead I associated with a vertical heart position were excluded. Included were tracings in which leads I, II and the left precordial leads had T waves of definitely less than 1 mm. amplitude down to those which were practically isoelectric, but not inverted. The same criteria were applied to leads aV_L and aV_F where the QRS was tall and mainly upright. In those cases where the heart is in the semi-vertical or semi-horizontal position and there is a small QRS, or a diphasic QRS, one normally expects a very low upright, isoelectric, or shallow inverted T wave. Of such cases we included in the minor T-wave change group only those showing inversion disproportionate to the QRS contour. We did not include those with a vertical heart and a negative T wave in aV_L or those with a horizontal heart and a negative T wave in aV_F. Notched T waves with no component below the isoelectric line, such as are illustrated in figure 9, were also included among the minor T-wave change group.

Some optimists might say that some of these T waves are within normal limits, but we do not think so. However, regardless of whether they are called normal, questionable or abnormal, they are samples of those included in the study. Here again, the individuals were normal in every respect except that their electrocardiograms showed abnormal or questionable T waves.

We found records on 273 individuals fulfilling the requirements, considering only males between the ages of 40 to 69 with an average age of 50 years. During the subsequent observa-

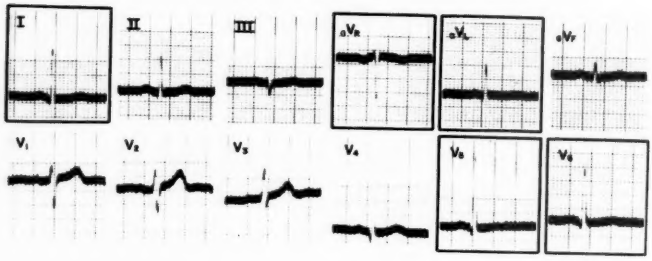

Figure 7

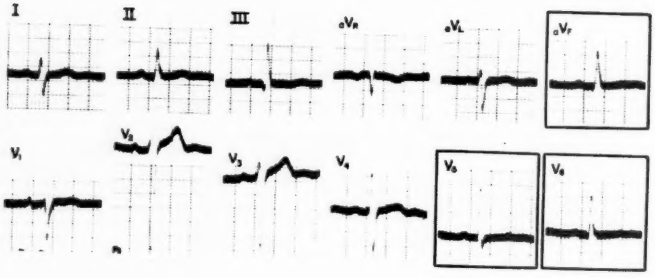

Figure 8

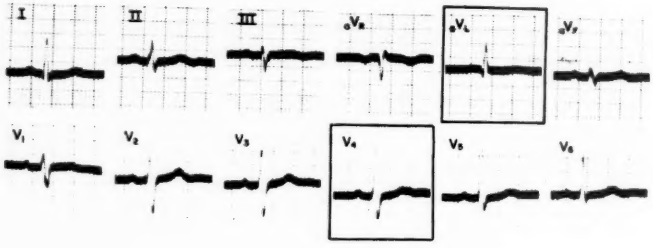

Figure 9

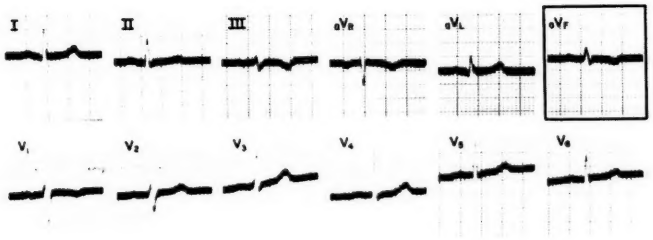

Figure 10

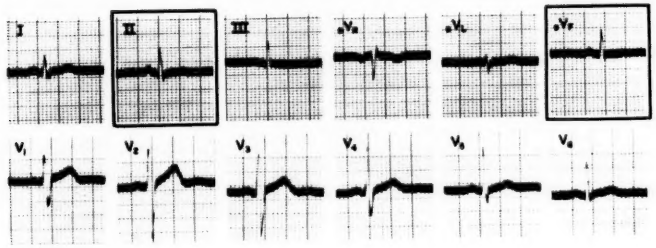

Figure 11

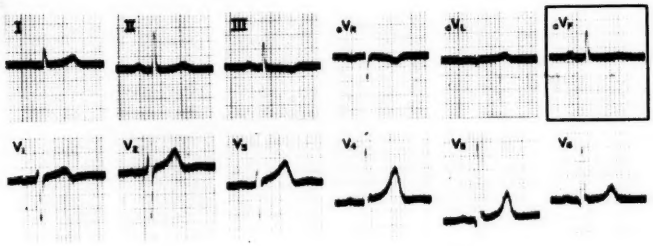

Figure 12

tion period of 6.6 years, 10.6 per cent developed coronary occlusion. There were 17 deaths expected but 29 actually resulted, giving a mortality ratio of 165 per cent or approximately twice the mortality of the normal control group. Of the 17 deaths, 65.5 per cent were caused by cardiovascular disease.

Table 4

Analysis by Groups

Group	Total Number	Deaths	Per Cent Actual to Expected Deaths	Per Cent Deaths from Cardiovascular Causes	Per Cent Total Number Subsequently Developing Coronary Occlusion
Normal	1,388	75	84	47	3.2
Minor T-wave changes	273	29	165	65.5	10.6
Major T-wave changes	43	7	302	71.4	16.3
Previous coronary history	112	40	526	95	—

The question arose whether or not T-wave changes in any particular lead or leads, such as the standard leads, unipolar extremity leads, or the precordial leads, were associated with the increased incidence of coronary occlusion and increased mortality. There is no evidence of this in the minor T-wave group. No particular pattern or lead was associated with the adverse experience. It is especially noteworthy that T-wave abnormalities in the unipolar extremity leads alone seem to be just as significant as T-wave changes elsewhere in the minor T-wave group. The major T-wave group was not large enough to permit study of this feature.

We found 39 additional cases which showed minor T-wave changes, such as illustrated here, but these were not included because the individuals related a history of chest pain which may have been angina pectoris. When we included these 39 cases with the original group of 273 the result was an additional 7 deaths, producing a mortality ratio of 165 per cent.

It is to be noted that adding the 39 cases having a history of suspicious chest pain did not alter the mortality. We cannot adequately explain this. Perhaps the 39 additional cases did not contain enough cases of true angina. It is very difficult to evaluate a history of chest pain and great care was used in order to exclude from the group for the study all those with suspicious chest pain. Perhaps these T-wave changes are just as significant of themselves as anginal chest pain.

While we feel that the results of this study are consistent, we do not claim that the data are conclusive. The groups are small. They always are in a study of this type. The period of follow-up is short, averaging six to seven years. However, we personally feel that in considering degenerative cardiovascular disease, which is by far the major cause of death among these individuals, one does not have to wait very long to obtain a significant mortality. It is, of course, possible that with longer periods of observation the mortality in all groups might increase.

Finally, these individuals are Prudential Insurance Company Home Office employees — not insurance applicants. The medical data is complete and we think it is safe to assume that little, if any, medical history has been withheld from the Employee Health Section staff physicians, who examined all of them. One may guess that in a group of applicants for insurance some could easily withhold pertinent information, and as a result the mortality associated with such T-wave changes might be higher.

What do these observations mean? We all know that in an individual case the electrocardiogram has little, if any, prognostic value. But, we also know that a questionable or abnormal T wave might be the only evidence of latent cardiovascular disease. Being aware of the limitations of this investigation we believe it is possible to draw certain valid conclusions. Groups of individuals showing T-wave changes, even though slight, will show an increase in mortality. There will be more cardiovascular disease in such groups than in groups which do not have similar T-wave changes. The more pronounced the T-wave changes, the greater the possibility that they indicate cardiovascular disease. After all, an increase in premium rate because of T-wave changes is actually based on the possibility that these

signify cardiovascular disease. It is recalled that all these individuals appeared to be normal otherwise. Could it not be inferred that if an applicant for life insurance should show other evidence of cardiovascular disease, such as hypertension or a murmur, the T-wave changes, even though slight, might take on even greater significance?

We do not propose that any underwriter in considering electrocardiographic deviations should automatically assess each case showing T-wave abnormalities with the mortality shown here. Certainly, consideration should be given to age and sex. We have good reason to believe that males below the age of 40 years do better as risks than those within the age range studied and this is true also for females of all ages. One might likewise be influenced favorably by a long period of stability, or unfavorably by recent instability of the abnormal T waves. We are uncertain about the importance of this. We believe, however, that an associated adverse family history might increase the mortality ratios shown. The same might apply to minor deviations from the normal cardiovascular system which require no increase in premium rate *per se*. These are some of the factors which must be considered in evaluating these T-wave changes.

We have shown a graded morbidity and mortality from the normal through the minor and the major T-wave groups to the group known to have had coronary occlusion. However, it is important to remember that there is a heterogenicity within each of the two abnormal T-wave groups in reference to the extent or degree of abnormality. There may very well be a degree of abnormality within each group which, if studied separately, would produce a lower or higher mortality ratio than that shown by the group as a whole. Of course, if one should remove from a group the individuals showing lower mortality than the entire group, the mortality of those remaining will be correspondingly increased and vice versa.

It is possible, of course, to make a division into minor and major T-wave abnormalities by other criteria than those employed here. For example, there are a few cases of isolated inverted T waves in leads aV_L and aV_F with a tall upright QRS, which were classified as a major T-wave change but might have been

put in the minor T-wave group. There were too few of these to study separately and we do not know how they compare with the entire major T-wave group. When confronted with T-wave abnormalities accompanying a tall upright QRS we arbitrarily used the isoelectric line in making the division between minor and major T-wave change.

Keeping these modifying features in mind, our figures may provide a starting point whence one can begin to evaluate the case as a whole. However, we doubt that many such cases are any better in the matter of risk than our figures would indicate. They might be considerably worse.

We gratefully acknowledge the valuable assistance of Miss Hazel H. Wallace and Mr. Lionel W. Oliver in this investigation.

PRESIDENT WILLIS — Thank you, Dr. Kiessling, Dr. Schaaf and Miss Lyle, for this splendid paper. The subject is one that has caused us great concern for a long time. I am sure that your findings will be of great help to us in the future.

DR. B. T. D. SCHWARZ — Dr. Kiessling has made a very fine contribution and I would like to ask him one question.

In one of the electrocardiograms he showed, the aV_F lead showed a very slight, almost isoelectric but inverted T wave, and in lead III, there was also a very slight inversion but more definite in aV_F. All the other T waves were satisfactory. You included that as one of the minor T-wave changes, and I wonder on what grounds you would base this as being abnormal rather than negative, since you finished up your concluding statement by saying that you felt that the rating would probably be 165 per cent or worse, perhaps. I wonder if that is not unduly severe on that particular case.

DR. KIESSLING — Let me show you here on the blackboard the group that we called minor T-wave changes. That is the most confusing group.

In general, we arbitrarily decided to call minor T-wave changes T waves which were disproportionately low but upright in lead I, lead II, and the left precordial leads. We also included upright but low T waves in aV_L with a tall upright QRS as one sees

in a horizontal heart or a tall upright QRS in aV_F as one sees in a vertical heart.

In hearts of the semivertical or intermediate position one normally sees a smaller R wave in aV_L or even a biphasic QRS. Here the T wave is low upright, isoelectric or even slightly inverted normally. Any disproportionate inversion was considered a minor T-wave change. The same applies to aV_F in semihorizontal hearts.

Major T-wave changes were those where the T wave was abnormally inverted in leads I, II or the left percordial leads. Likewise, in aV_L with a tall upright QRS as one sees in horizontal hearts or in aV_F in vertical hearts, any inversion was considered a major T-wave abnormality.

Does that explain the situation any better?

DR. SCHWARZ — Yes, it does.

DR. RICHARD S. GUBNER — I would like to ask you, Dr. Kiessling, whether any attempt was made to alter the natural course in these various categories of abnormalities. The reason I ask this is that something as simple as a low fat diet, at least from the observations of Morrison, very materially reduces the subsequent mortality of people who have had coronary occlusions. Have any of these people among your employees been advised to alter their way of life, in terms of diet or other therapeutic measures? If so, this would, of course, more favorably influence your figures than the ones that we encounter in our routine underwriting practice.

DR. KIESSLING — As far as I know treatment did not enter into the consideration of these cases. I cannot answer that question completely but I think that feature can be disregarded in the evaluation of these statistics.

DR. GUBNER — You did not give therapeutic advice to these employees, then?

DR. KIESSLING — No. In fact, most of the individuals who showed minor T-wave changes, we treated as a clinician would. We noted it, saw them again at the end of a year or two, and until something developed clinically, we paid very little attention to minor T-wave changes.

DR. GUBNER — How about the major ones?

DR. KIESSLING — Let me recall to your mind that these individuals were all normal clinically. When we saw even major T-wave changes we again noted the finding, made additional inquiries about past history or symptoms. None being present, we took no definite action and made no diagnosis of heart disease, although I am sure we felt in many cases that such was present. In general, we took great pains not to alarm these individuals and tell them they had heart disease on the basis of electrocardiographic findings alone, and that is what all of these cases were, isolated electrocardiographic findings.

DR. M. HENRY CLIFFORD — Along that same line, just to confirm it, I assume that the electrocardiograms you have used represent changes of a minor or major T wave, as the case might be, that were persistent either throughout the years or persistent at that time.

DR. KIESSLING — No, some of the changes were persistent, and we saw them through a series of records and through a series of several years. Other changes appeared on just one record, and then, a year later, they were gone, so we could make no distinction between the evanescent changes and the persistent findings. Every time you divide these groups into sub-divisions, the groups become smaller and they become worthless statistically. Some day, we will be able to have a large enough group to make divisions such as that.

DR. B. T. D. SCHWARZ — Would you regard the very minor T-wave changes as possibly being due to functional or physiological changes, if a succeeding electrocardiogram showed the T-wave abnormality corrected?

DR. KIESSLING — Perhaps. I do not think that all these people have heart disease. Many of these changes are functional or non-cardiac. We know that a spontaneous pneumothorax will alter T waves across the precordium. A heavy meal, maybe too much smoking, or innumerable conditions may cause T-wave changes. If every T-wave change signified that an individual had changes in the coronary circulation, the job of selection would be easier.

If you take a group showing these T-wave changes, that group will contain individuals whose T-wave changes are physiological, individuals whose T-wave changes are secondary to non-cardiac disease and individuals whose T-wave changes are manifestations of cardiac pathology, usually degenerative. While we cannot separate them by means of an electrocardiogram, we do know that this group will contain more cardiovascular disease than a group not showing these changes.

DR. MURRAY F. BELL — Dr. Kiessling, did you include any of those cases which had a T wave in a complex, succeeding a ventricular extrasystole, and were inverted, whereas the T waves in the remainder of the leads were upright? And, also, what was done in those cases in which the T wave in a single lead changes, being upright and normal in amplitude in some of the complexes, and shading off and flattening in others?

DR. KIESSLING — We did not include T-wave changes following premature or ectopic beats and we did not include T waves which shaded off or flattened in a few beats as one sometimes sees in respiratory variations.

DR. EUGENE V. HIGGINS — You have not mentioned it at all, and I do not know whether your work included exercise tests, but would the tracing after exercise be of any value in distinguishing between those changes which were significant and those changes which were insignificant?

DR. KIESSLING — I do not know whether the exercise test would separate them because we have not done a sufficient number to make a study of our exercise tests worthwhile.

DR. HIGGINS — We have had such cases and I have occasionally asked for it, and sometimes I though it had been helpful. If you get a very good test, with no evidence of trouble at all, you may accept the minor changes as being more likely physiological.

DR. KIESSLING — Yes. I think if you considered any group of individuals, whether or not they showed abnormal T-wave changes, and selected those who had normal exercise tests, you would have a better group. I am sure that the same would hold true for people who show T-wave changes.

DR. DAVID J. BREITHAUPT — Of your employees who had electrocardiograms, was there any selection or was an electrocardiogram done on every one who came to your clinic?

DR. KIESSLING — These were mainly routine electrocardiographic examinations. Some of the employees might have come to the Health Section because of symptoms but complete physical examination revealed no evidence of cardiovascular disease. Those that had chest pain in any way suggestive of angina were excluded. Many of the tracings were made as part of a routine periodic physical examination. I want to stress again that the individuals that made up this study were normal individuals as far as we could determine and the electrocardiographic findings were isolated.

DR. HARRY E. UNGERLEIDER — Did you see many notched T waves in the peak of the T wave of the precordial leads in your series?

DR. KIESSLING — Yes, we had a considerable number of such tracings.

DR. UNGERLEIDER — Where did you place those?

DR. KIESSLING — The notched T waves?

DR. UNGERLEIDER — In the peak of the T wave — not to give you any negative quality.

DR. KIESSLING — I know what you mean. Notched T waves were included among the minor T-wave changes.

DR. ROBERT J. OEHRIG — Clinically, one would tend to be a little more suspicious of those showing minor T-wave changes in multiple leads rather than in one, and, yet, I think I understood you to say that you made no differentiation. Is that correct?

DR. KIESSLING — Yes, that is right.

DR. OEHRIG — The other thing I wanted to ask is, one tends to make some allowances for build and for the type of machine used when minor T-wave changes are present. I personally am more suspicious of a flat T wave in someone who has a thin chest wall than in one who has a thick chest wall. I do not know if your study made allowances for that.

Finally, were these tracings all taken on a string galvanometer?

DR. KIESSLING — We did not take build into consideration. All the tracings were made on a string galvanometer.

PRESIDENT WILLIS — The problem of classifying life insurance risks with hypertensive disease is an old one in the industry. With the advent of the new drugs in the treatment of hypertension, the problem has become more difficult. I am pleased to have a paper presented, the title of which is, "Some Aspects of the Development and Treatment of Hypertensive Disease." The author is Dr. Edgar A. Hines, Jr., Professor of Medicine, Mayo Foundation, Graduate School of the University of Minnesota, and head of the Section of Medicine at the Mayo Clinic.

SOME ASPECTS OF THE DEVELOPMENT AND TREATMENT OF HYPERTENSIVE DISEASE*

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Section of Medicine,
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This presentation will consider the variability of blood pressure, the reactions and hyperreactions of blood pressure, and some of their probable relationships to the subsequent development and treatment of hypertension.

Normal Blood Pressure

Blood pressure is variable in all persons. It varies from minute to minute, hour to hour and day to day; as is now known from extremely sensitive and accurate direct recordings of blood pressure, it may even vary slightly from second to second. It is this inherent variability that makes it so difficult to establish the range of normal blood pressure or even to determine, in each person, the exact degree of variations of the blood pressure to which he is subjected in normal daily routine and in the stresses of emotion, work and fatigue.

For purposes of clarification, definitions of some basic terms used in describing blood pressure and its variability are presented in tables 1 and 2. Most physicians, of course, are familiar with these terms but it is well to bear them in mind when variability and reactions of the blood pressure are being considered.

The three definitions of normal blood pressures shown in table 1 convey my own ideas. The definition ordinarily used in published studies is the first, which is the statistical definition. It gives valuable information concerning the range of blood pressure in groups of persons but it is not too helpful when physicians are

*Read at the meeting of the Association of Life Insurance Medical Directors of America, Statler Hotel, New York City, October 19, 1955.

†The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

TABLE 1

DEFINITIONS OF NORMAL BLOOD PRESSURE

Statistical definition

The commonest blood pressure found in persons of average weight and of a certain age

Physiologic definition

The blood pressure necessary to keep all tissues and organs of the body functioning efficiently in all natural positions and in all forms of necessary physical activity

Clinical definition

The desirable or ideal blood pressure indicating a healthful or potentially healthful state

TABLE 2

DEFINITIONS CONCERNING MEASUREMENTS AND VARIABILITY OF BLOOD PRESSURE

Basal blood pressure

The blood pressure recorded when all emotional, physical and metabolic activities are reduced to a physiologic minimum

Casual blood pressure

The blood pressure obtained during physical examination without use of any special means to minimize emotional, physical and metabolic activities

Supplemental blood pressure

The difference between basal and casual blood pressure or between basal and maximal blood pressure during a standard pressor test (cold pressor test; breath-holding test)

dealing with individual patients and trying to decide whether or not a given patient has a "normal" blood pressure, particularly when the values are in what might be called the borderline ranges.

The excellent statistical work by Master and others has been of help, but physicians still are faced with the problem of determining what degree of deviation from the statistical average surely indicates that an individual patient's blood pressure is unhealthily high or low. In my opinion, this is still a hypothetic measure. Honest and logical application of this particular definition to its conclusion leads to another unanswered question, "What is significant hypertension?"

What the physician needs most to know is what range of blood pressure is healthful or potentially healthful for his patient and what values, particularly in the borderline ranges, necessitate treatment. Unfortunately, specific answers to these perplexing questions are not available. Definite answers await follow-up studies of large groups of unselected persons for periods of 10 to 30 years, during which the basal blood pressures, supplemental blood pressures and the blood-pressure reactions have been recorded at appropriate intervals. In the absence of adequate follow-up studies of this type, final conclusions cannot be drawn as to the significance of borderline blood-pressure readings or hyperreactivity of the blood pressure.

Development of Hypertension

This presentation is based on what knowledge I have concerning hyperreactivity of blood pressure and its possible significance. Forewarning is given that these opinions are not based on an adequate follow-up study of a sufficiently large group of unselected persons.

The variability of the blood pressure can be measured in two ways. One is by determining the blood pressure every half hour or hour during periods of rest and normal activity of a person and comparing the basal blood pressure to the maximal value. The other method consists of using some form of a pressor test. The cold pressor test is a standard technic in which a cold stimulus is applied; the maximal increase in the blood pressure from a basal level as a result of application of the cold stimulus then becomes a measure of the variability of the blood pressure.

TABLE 3

TERMS USED TO DESCRIBE PERSONS AND THEIR BLOOD-PRESSURE REACTIONS

Hyporeactor

A person who has a supplemental blood pressure of less than 10 mm. of mercury systolic or diastolic or both

Example: 100/60 — 108/66 = +8/6

Normoreactor

A person who has a supplemental blood pressure between 10 and 20 mm. systolic or diastolic or both

Example: 110/70 — 125/80 = +15/10

Hyperreactor

A person who has a supplemental blood pressure greater than 20 mm. systolic or diastolic or both

Examples: 110/70 — 150/80 = +40/10
110/70 — 150/100 = +40/30

TABLE 4

MORE TERMS USED TO DESCRIBE PERSONS AND THEIR BLOOD-PRESSURE REACTIONS

Cardiac hyperreactor*

A person who has a hyperreaction only in systolic blood pressure (usually accompanied by an increase in heart rate)

Example: 110/70 — 150/80
Pulse 84 — 106

Vascular hyperreactor†

A person who has a hyperreaction in diastolic blood pressure (usually accompanied by an increase in systolic blood pressure and little change in heart rate)

Example: 120/75 — 160/100
Pulse 80 — 86

*Caused by an increase in cardiac output.

†Caused by peripheral vasoconstriction.

The reactions of blood pressure induced by the pressor test or determined by hourly readings of blood pressure allow persons to be grouped roughly into three types, namely hyporeactors, normoreactors and hyperreactors table 3). These are arbitrary groupings whose definitions have varied from time to time.

Two important types of hyperreactivity to blood pressure are defined in table 4. The cardiac hyperreactors shows a hyperreaction in systolic blood pressure alone, which usually is accompanied by an increase in the heart rate. The vascular hyperreactor is a person whose hyperreaction is largely due to an increase in peripheral vasoconstriction and resistance rather than to an increase in cardiac output. This type of hyperreaction should be measured largely by the change in the diastolic blood pressure as distinguished from a change in the systolic blood pressure alone. Of course, most diastolic hyperreactors also have hyperreaction of the systolic blood pressure.

Some evidence exists that the cardiac type of hyperreaction is not in itself significant of a subsequent development of diastolic hypertension or of any hypertensive disease. Follow-up studies were made on a group of patients who had what might be called a "psychic pressor test."* Among this group were 148 patients who had systolic blood pressures more than 140 mm. of mercury but diastolic blood pressures less than 80 mm. None of these 148 patients had diastolic hypertension 20 years later or any hypertensive changes in their ocular fundi or any evidence of hypertensive vascular disease. Although this is a relatively small group, the results indicate that a systolic hyperreaction alone is not indicative of later occurrence of diastolic hypertension in the majority of persons.

There is some evidence that variability and hyperreactivity of the diastolic blood pressure, within the so-called borderline range,

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*This was a group of patients on their first visit to the Mayo Clinic and whose initial blood-pressure reading was recorded by a strange doctor in strange surroundings. This initial recording was correlated with the development of hypertension when the patients returned to the clinic 20 years later. All these patients had blood pressures that might have been considered within the normal range on their original examination.

TABLE 5

INCIDENCE OF SUBSEQUENT HYPERTENSION ACCORDING TO ORIGINAL (NORMAL) DIASTOLIC BLOOD PRESSURE*

Classification†	Cases	Hypertension 10 or 20 years later	
		Cases	Per cent
Hyporeactors	198	0	0
Normoreactors	878	31	4
Hyperreactors	446	254	57

*Diastolic blood pressure always less than 100 mm. of mercury.

†Hyporeactor = maximal diastolic pressure less than 70 mm. of mercury; normoreactor = maximal diastolic pressure 70 to 84 mm.; hyperreactor = maximal diastolic pressure 85 to 99 mm.

TABLE 6

REACTION OF NORMAL DIASTOLIC BLOOD PRESSURE TO THE COLD PRESSOR TEST CORRELATED WITH THE SUBSEQUENT DEVELOPMENT OF HYPERTENSION*

Classification†	Cases	Hypertension 15 years later	
		Cases	Per cent
Hyporeactors	36	0	0
Normoreactors	48	8	17
Hyperreactors	57	31	54

*Diastolic pressure always less than 100 mm. of mercury except during the cold pressor test.

†Hyporeactor = increase of less than 10 mm. of mercury; normoreactor = increase of 10 to 20 mm.; hyperreactor = increase of more than 20 mm.

are of significance in the development of hypertensive disease. Table 5 shows a follow-up of the entire group of patients in whom the first reading of blood pressure was used as a measure of response to a psychic pressor test. This initial reading then was correlated with the subsequent occurrence of hypertension 10 or 20 years later. The patients were classified as hyporeactors, normoreactors and hyperreactors according to their maximal diastolic blood pressure; thus, the grouping in this instance is different from that defined in table 3. In this group, the hyporeactors did not have diastolic hypertension 10 or 20 years later. A small number of the normoreactors had diastolic hypertension and 57 per cent of the hyperreactors had significant diastolic hypertension 10 or 20 years later.

Table 6 shows a follow-up of a similar nature but on persons who had had normal blood pressures when they had been subjected to the cold pressor test 15 years previously. The hyporeactors in this group did not have hypertension 15 years later, whereas 54 per cent of the hyperreactors did have hypertension 15 years later. The reactors in this group were defined according to the criteria in table 3.

Hereditary Factors in Hypertension

Space does not allow discussion of all the factors that might be related to variability of blood pressure or its hyperreactions or hyporeactions. A number of physiologic and other factors are involved. Consideration will be given to the probable role of the hereditary factor in this variability and reactability.

Table 7 presents an analysis of the afore-mentioned large group concerning whom statements were made on the original clinical history as to whether or not their parents had hypertension. Diastolic hypertension then was looked for when they returned to the clinic 10 or 20 years later. The incidence of diastolic hypertension 10 or 20 years later was seven or eight times as great among those who gave a positive family history as it was among those who had a negative family history.

TABLE 7

INCIDENCE OF SUBSEQUENT HYPERTENSION ACCORDING TO FAMILY HISTORY

Category	Cases	Subsequent hypertension	
		Cases	Per cent
Ten-year follow-up			
Positive family history	182	59	32
Negative family history	496	22	4
Twenty-year follow-up			
Positive family history	254	113	44
Negative family history	442	33	7
Total	1,374	227	17

Table 8 gives data in another group separated from the original large group because they had various types of renal disease. Some of the patients in groups 1 and 2 in this table had no significant organic renal disease, whereas some of those in group 3 had had bilateral atrophic pyelonephritis for a number of years. Follow-up studies in this group of patients revealed that the subsequent development of hypertension was correlated more closely with a positive or negative family history of hypertension than it was with the degree of renal involvement.

Studies of the blood pressures and blood-pressure reactions have been done on families in and around Rochester in which I personally have evaluated the reactability of the blood pressure of all living members of these families. A few representative families from this study will be mentioned. One group consisted of a father and six children. The three older children had hypertension and the three younger children were hyperreactors; 8 years later, all the children, including the three hyperreactors, had hypertension.

TABLE 8

INCIDENCE OF SUBSEQUENT HYPERTENSION ACCORDING TO FAMILY HISTORY AND EXTENT OF RENAL INVOLVEMENT

Category	Cases	Hypertension at last visit	
		Cases	Per cent
Family history of hypertension			
Positive	61	41	67
Negative	124	22	18
Unknown	79	29	37
Extent of renal involvement			
Group 1 (bacilluria, normal urograms)	32	12	37
Group 2 (unilateral renal disease)	104	31	30
Group 3 (bilateral renal disease)	128	49	38

Every person in a larger family group had normal blood pressures and were normoreactors. Two large family groups were studied in which normal blood pressures and normal reactions were present on one side of the family tree and hyperreactors and hypertension were present on the other side. The same situation prevailed in two other large families. One of the men with normal blood pressure married a woman who was a hyperreactor; some of their children were hyperreactors.

Worth-while information about hereditary factors in blood pressure can be gained by studies of twins. A few studies concerning single blood-pressure readings have been done on twins, but I do not know of any previous studies in which basal blood pressures

and hyperreactions of the blood pressure to a standard pressor test have been evaluated in a fairly large group of twins. Conclusions regarding the possible factor of heredity are drawn from determining whether or not identical twins have more nearly identical basal blood pressures and reactions to the cold pressor test than do fraternal twins.

McElheny, Gage and I have under way a statistical survey of blood-pressure studies, including cold pressor tests, on 200 sets of twins. The following represents some of the preliminary observations. Table 9 shows the average differences in blood pressure between the twins in each set. The identical twins have much more nearly identical basal blood pressures and reactions of their blood pressures than do the fraternal twins. This is further evidence

TABLE 9

*DIFFERENCES OF BLOOD-PRESSURE READINGS IN MILLIMETERS OF MERCURY IN 200 SETS OF TWINS**

Blood pressures	Twins	
	Identical (87 sets)	Fraternal (113 sets)
Systolic		
Basal	4.1	7.6
On cold pressor test		
Maximum	6.2	11.1
Increase	5.7	8.4
Diastolic		
Basal	3.5	5.6
On cold pressor test		
Maximum	5.0	9.3
Increase	5.0	8.0

*Distribution: Minnesota, 61 sets; Tennessee, 46 sets; Texas, 93 sets.

that a hereditary factor is concerned with the mechanism that controls blood pressure in persons who have normal blood pressure and probably in those who have increased blood pressure.

Classification of Diastolic Hypertension

Is there any way out of the dilemma of what to do with the hyperreactor or the patient who has a diastolic blood pressure in the borderline range? This question cannot be answered definitely at present. However, a suggestion can be made concerning how these hyperreactors may be classified. Table 10 is an oversimplified classification of diastolic hypertension. The vascular hyperreactors are not placed in the group with essential hypertension but are in a separate category. No conclusions can be drawn so far as an individual patient is concerned as to what such a hyperreactive blood pressure means or as to what it will mean within a few years. Such vascular hyperreactors should be followed without any attempt at specific antihypertensive treatment until a more persist-

TABLE 10

TENTATIVE CLASSIFICATION OF DIASTOLIC HYPERTENSION

Diastolic hypertension, or hypertensive disease
(increased peripheral resistance)

Vascular hyperreactor

Latent hypertension

Essential hypertension
(diffuse arteriolar disease)
Groups 1, 2, 3, 4

Secondary hypertension
Coarctation of aorta
Pheochromocytoma
Atrophic pyelonephritis
Glomerulonephritis
Cushing's syndrome

ent diastolic hypertension has occurred or other signs of hypertensive vascular disease have developed.

Treatment

The ideal time to start the treatment of hypertension is during the preorganic stage. However, as already intimated, no yardstick is available for determining what will happen to the vascular hyperreactors and patients who have mild essential hypertension if they are not treated, because an unselected mildly hypertensive group has not been followed long enough to allow any conclusions as to the results in this group following sympathectomy or use of the newer drugs. My present feeling, as mentioned previously, is that vascular hyperreactors and patients who have mild essential hypertension should not be given intensive treatment but should be observed until there is some evidence of increasing diastolic blood pressure or progression in their hypertensive vascular disease.

The following case illustrates the dilemma in this particular group.

In 1928, a 28 year old man had a blood pressure that ranged between 145/95 and 160/100. Results of funduscopic examination were normal. He had a normal electrocardiogram and a normal-sized heart. With present knowledge, I would call this person a vascular hyperreactor. However, he was told that he had serious hypertensive disease for a person of his age, which at that time might have been a reasonable conclusion.

He applied for and received from his insurance company payments of $200 a month for permanent total disability. I examined him at his home city in 1940, when he was 40 years of age, which was 12 years after the hypertension was first discovered. His blood pressure had ranged during that time between 150/90 and 165/110. Results of the funduscopic examination still were negative except for extremely slight narrowing of his retinal arterioles. He died in 1952, at the age of 52, of a coronary occlusion, which was his first vascular complication. His blood pressure never had been recorded as more than 170/110.

Any treatment would be considered to have given excellent long-term results for this patient, whereas he actually received no treatment during these 25 years, unless the disability pension could be considered a form of psychotherapy.

The many combinations of newer drugs now available for the management of hypertension are really bewildering. The 1955 edition of the *Physicians' Desk Reference* listed about 48 combinations of hexamethonium, hydralazine (apresoline) and the Rau-

wolfia drugs; 80 preparations are listed as useful for the treatment of hypertension.

The drugs in current use generally are of three types. The first type includes those of the Rauwolfia group, with a predominant effect on the midbrain. The second type comprises those which produce peripheral block of the sympathetic nerves, such as hexamethonium, pentolinium tartrate (ansolysen) and chlorisondamine dimethochloride (ecolid). Incidentally, these drugs also block the parasympathetic nerves, which is why difficulty arises from their side effects. The third but smaller group of drugs, such as hydralazine and the Veratrum group, apparently acts partly on the midbrain and partly peripherally.

Because these drugs have been used for only a short time, any evaluation of their current use in the medical treatment of hypertension must be considered as a clinical impression. Someone has said that physicians make the same mistakes a thousand times and call it "clinical experience." At any rate, since it is too early to come to any definite conclusion about the long-term effects of these drugs, the following opinions necessarily are confined to their short-term effects.

Actually, investigators are now going through the same stages with these drugs, particularly the sympathetic-blocking agents, that they already have been through with sympathectomy. It is reasonable to transfer some of the experiences with sympathectomy to the sympathetic-blocking drugs; perhaps on this basis the effects of the sympathetic-blocking agents can be extended over a little longer time than they actually have been used.

The results of sympathectomy as to survival can be stated and then an attempt can be made to transfer such data to some of the newer drugs. The incidence of death up to a 5-year follow-up period is about three times greater in patients who have group 2 or 3 hypertension and who have not had sympathectomy, than it is in patients of the same age in the same group who have had sympathectomy. The incidence of death is 50 per cent greater up to a 5-year period in untreated patients who have group 4 (malignant) hypertension than it is in like patients who have had sympathectomy.

Thus, in the more severe types of hypertensive disease, it can be concluded that sympathectomy has extended the life of some patients. I suspect that we may find the same results after some of the newer antihypertensive drugs have been used for 5 years.

As far as prognosis is concerned, the results of sympathectomy are better by about 15 or 20 per cent in women than in men; I suspect that similar results will follow use of the newer drugs. However, this difference in prognosis between women and men is about the same even if they are not treated.

Valid experience of up to about 3 years now is available in evaluation of the newer drugs in patients with group 4 (malignant) hypertension. Instead of an expected incidence of death of 95 per cent of these patients within this 3-year period, the incidence of death has been only 45 per cent in the group treated with the newer drugs, particularly hexamethonium and apresoline. My present guess is that the 5-year results of present methods of treatment with drugs will be similar to the 5-year results observed after sympathectomy if those patients who, for one reason or another, stopped treatment with these agents or reduced their dosage below an effective amount are considered as failures of treatment. Of course, improvements and changes are taking place all the time in antihypertensive drugs, and this statement might not be true even 2 or 3 years from now.

It is doubtful if use of these agents to decrease the blood pressure of patients who already have severe hypertensive disease will prevent or delay vascular complications, such as coronary or cerebral arterial occlusion. One group of investigators made a follow-up study of 61 patients who were treated with these newer drugs, principally hexamethonium and apresoline, for an average of 10 months; they did not find that these agents reduced or delayed such vascular complications.

I have studied 17 patients who experienced adequate control of their blood pressure from hexamethonium or apresoline or both for 2 years or more; four had coronary occlusion, which proved fatal in two of them.

The sympathetic-blocking drugs alone are helpful in relieving congestive cardiac failure caused largely by hypertension, and I

have little doubt that the newer agents, particularly these sympathetic-blocking drugs, if they adequately decrease blood pressure, will delay or prevent future occurrence of congestive cardiac failure in many patients. The situation with regard to the prevention of cardiac failure is a little different and more promising than that of the prevention or delay of arterial occlusion due to atherosclerosis in these groups.

Use of the currently available antihypertensive drugs is accompanied by some serious drawbacks. This point in the discussion presents a good opportunity to consider the future place of sympathectomy in the treatment of hypertension. The future use of sympathectomy belongs somewhere between the attitude of an eminent internist who said that sympathectomy for the treatment of hypertension was another example of the triumph of technic over reason and the attitude of the young neurosurgeon who thought that every young man who had a family history of hypertension ought to have a sympathectomy.

If it were possible to predict with certainty what individual patients would get good long-term results from sympathectomy, that operation would be a better method of treatment for patients with group 3 or 4 hypertension than would use of the sympathetic-blocking drugs available at present. This is because of the high cost of such drugs and because of what appears to be an increase in the "fall-out" rate, after 2 or 3 years, of patients who take these drugs. "Fall-out" rate refers to patients who, for one reason or another, often because of inconvenience or cost, either stopped the use of the drugs or decreased the dose so that it does not have any effect.

About the only patients I see now who will submit to sympathectomy are those who have tried the drugs and have not been satisfied with them or in whom the drugs have not been effective. The cost of continued use of these drugs is still great, which can be illustrated in an exaggerated way by the experiences of two of my patients. One patient, about 40 years of age, has had excellent control of his blood pressure since a sympathectomy was done 3 years ago. His blood pressure practically never has been more than 160/100 since the operation. The other patient was treated with a combination of drugs, consisting of injections of hexa-

methonium and large doses of apresoline taken orally. He has experienced excellent control of his blood pressure for a 3-year period. The patient who had the sympathectomy had a total cost, including everything, of $1,095; the patient who took the drugs for 3 years had a cost of $1,950. Thus, some people cannot afford to take these drugs if they need large doses of the more expensive preparations.

Another difficulty about drug treatment is that the sympathetic-blocking agents give good reduction in blood pressure only when the patient is upright. Unless the patient sleeps standing up, his heart and arterial vascular system are subjected to the same stresses and strains for a third or a half the time that they are if treatment is not given.

DR. JAMES R. GUDGER — Dr. Hines, would you like to comment on a practical laboratory method of detecting products of Rauwolfia used in the treatment of hypertension, say, in the blood stream or the body excretions?

DR. B. T. D. SCHWARZ — Dr. Hines, I am sure that you will not mind this little personal reference to my son, Bert, who is a fourth-year fellow at the Mayo Clinic in psychiatry. I believe he might agree with you that some of these hypertensives might be cured if their economic status would be helped, as you indicated. But I do not believe that he would go as far, perhaps, as the neurosurgeon who, you said, was itching to cure all cases of a hereditary hypertension by doing a sympathectomy on their offspring.

I would like to word my question and observation, however, direct to your statement, that the use of these hypertensive drugs is very helpful in heart failure, when the person has hypertension. I would like to ask what your experience is, because it has been mine, in a woman aged 60, who had a blood pressure well up in the 200s at least ten years to my knowledge, and a diastolic reading from 120 to 140, and, within the last nine months, when we instituted some serpasil therapy, she went into a state of heart failure, edema of the lower limbs, increased weight, marked lassitude and fatigue. Each time, we reduced the dose to just one milligram, as a matter of fact, but finally we had to take her

off it, and then she had a spontaneous recovery. We did this three times, and each time, the same procedure. What is your opinion on that case?

DR. A. E. PARKS — I should like to ask Dr. Hines whether he would think that a strongly positive family history of hypertensive disease would adversely affect his estimate of prognosis in an individual, otherwise healthy, who had either a normal blood pressure or one but slightly elevated, and who might be called a cardiac hyperreactor.

DR. R. A. GOODELL — I just want to say that the burning question with many of us is whether a person with hypertension, before he has the organic changes of hypertensive disease, has a better prognosis and is less likely to develop complications of hypertension if he is on the Rauwolfia products than if he were not? I wonder if Dr. Hines would care to hazard a guess.

DR. HINES — Dr. Willis has given me a tough task, and it is getting late.

Actually I am glad to stay here as long as you are, and try to answer the questions. With regard to the first question, I do not know of any practical laboratory method for determining the concentration of the Rauwolfia preparations in a patient who is being treated with them. Dr. Gudger may be thinking of bioassays, and there is some work being done along that line, but as far as I know, it has not reached the stage where it can be used routinely in the clinical laboratory. It might be of help, however, if we did have something like that because, as you well know, during the early years of thiocyanate therapy, many patients had bad reactions from it and it was to a large extent stopped because the incidence of bad side effects was so great. Well, when we had a method of measuring the concentration of thiocyanate in the blood we found that most of these patients were not ill because they were sensitive to the drug but because they were getting too much of it. But we do not have this type of control of the Rauwolfia drugs as yet. If you know of any test, I would be glad to learn of it.

When I referred to the hypertensive drugs as being of help in patients who have congestive heart failure, I was referring par-

ticularly to my own experience with the sympathetic blocking drugs such as hexamethonium or ansolysen. In those patients with congestive heart failure who have had a significant lowering of their blood pressure from these drugs, I have found them helpful in relieving their congestive failure. I have not found the Rauwolfia drugs or even apresoline to be nearly as helpful as the sympathetic blocking drugs in congestive heart failure. In fact apresoline probably should not be used in patients who have serious heart disease or heart failure, because one of the effects of apresoline is to increase cardiac irritability and produce tachycardia.

The question of edema and of the initiation of congestive heart failure in patients who are taking Rauwolfia is an interesting one. I have not seen or have not recognized the initiation of heart failure in any of my patients who have taken the Rauwolfia drugs but I have seen several patients who had edema of the lower extremities, not due to congestive heart failure, who had a marked increase in their edema when they were given Rauwolfia drugs for their nervous-tension states.

There is some experimental evidence that the Rauwolfia drugs increase the effect of the antidiuretic hormones and it is possible that they might, through this effect, increase the tendency for congestive heart failure to develop. That is purely hypothetical as yet.

I do not know the answer to the question as to whether a strongly positive family history would affect the prognosis in a purely "cardiac hyperreactor." No follow-up studies have been done along that line. The only way to obtain this information would be to follow up a group of "cardiac hyperreactors" and see how many of them with strongly positive family histories might have developed hypertension. But, on second thought, I would guess that, on the basis of my own follow-up studies in which I found that none of the cardiac hyperreactors have developed diastolic hypertension in 20 years, it might not make any difference what the family history was, because none of this small group of cardiac hyperreactors had developed hypertension anyway.

I suspect that the family history would not be of significance in a purely "cardiac hyperreactor" (unless both the mother and

father had hypertension). If both the father and mother had hypertension it might be of some prognostic significance in the cardiac hyperreactor, because in this entire group that we studied, there were 58 patients who stated on their first examination, at a time when they had normal blood pressure, that both their father and mother had hypertension. This was just a statement on the family history that "father has hypertension and mother has hypertension." Twenty years later, 54 of those 58 had diastolic hypertension and there may have been one or two cardiac hyperreactors in this group.

The last question was about the likelihood of the development of complications while the patient is taking Rauwolfia drugs. I am afraid I will have to have that question again.

DR. GOODELL — I just wanted your opinion as to whether the moderate hypertensives who are now on Rauwolfia have a better prognosis than those who are not.

DR. HINES — I cannot answer that, because we would have to have a follow-up to find out, and we do not even have a follow-up of the hyperreactors and mild hypertensives who are not on treatment that is adequate for comparison. My guess is that it is doubtful whether it would affect their prognosis, even if they were treated with the Rauwolfia drugs for a long time. The reason I do not treat patients who have been classified as vascular hyperreactors or who have mild essential hypertension with these newer drugs and particularly with Rauwolfia drugs is that they may get serious complications from the Rauwolfia drugs, with nervous tension and depression states, occasionally requiring shock treatment or other forms of psychotherapy extending over a long period. In some of these patients a mild parkinsonism develops.

One trouble is that as yet we do not know how often such serious complications happen to these patients receiving Rauwolfia drugs. My personal feeling is that until we know much more about the side reactions of these drugs, and since these patients who have vascular reactions or have mild hypertension will probably get along satisfactorily for a number of years or a few years anyway, I would rather not treat them with the newer

drugs until I know more about just what such drugs do or might do over a period of a greater number of years.

There are other people who have a different opinion. There are some who would treat a patient who has mild hypertension with the Rauwolfia drugs. Maybe they are right and I am wrong. But I just cannot bring myself to do that, especially since we have found that Rauwolfia is not entirely harmless and innocuous, as was at first thought by everybody.

PRESIDENT WILLIS — We have time for one or two more questions.

DR. KARL W. ANDERSON — Dr. Hines, there is a problem that has always bothered me. When do you tell a patient that he has hypertension? One case came to my office with 150/100, fifth phase diastolic. I suggested that he go down to the Mayo Clinic. In the meantime, we had suggested and offered a substandard policy, because of his blood pressure of 150/100. I got a report back from one of your colleagues, in which he said that the blood pressure of 150/100 was perfectly normal. The patient came back to me and said, "I am perfectly normal. Therefore, I will not take your substandard policy."

It is very irritating, let us say, for someone to say it is perfectly normal to have a blood pressure of 150/100 and another one say, "This is substandard." When does the clinic say, or what figures do you use when you say, to your patient what is normal and what is not normal? It would help us materially.

DR. HINES — Dr. Anderson, as far as the clinic is concerned, we have a private practice of medicine as you know, and each physician at the clinic forms his own opinion and gives his own opinion as to what he thinks about the patient whom he has seen. There is no set of official standards that the Mayo Clinic uses to define a blood pressure which is too high or too low.

If the patient has come to the clinic and I see him because he has hypertension or because he has been told that he has hypertension, then I believe that I have to tell that patient something definite about his blood pressure. If he has a maximal blood

pressure of 150/90 or 150/100 and maybe I have done a cold pressor test on him and that is as high as his blood pressure goes, I tell him just what I have been telling you here. I try to tell him in a very condensed, informal and simple way that he is a vascular hyperreactor, and I do not know what that means in the future in his particular case. I tell him that we do know that a good many of these hyperreactive people do eventually have significant diastolic hypertension, but I cannot tell him whether he is going to have it in the next year or the year after or for many years. I do tell him that it is not anything at the moment to be seriously concerned about but that he does have an abnormality. He cannot be considered as being entirely 100 per cent normal. I tell him that I do not think he should be treated now but that he should have his blood pressure checked from time to time, perhaps every six months or yearly, to determine whether the situation has changed and if something different should be done about it.

I do not believe that that patient will go from me to you with the idea that he is 100 per cent normal, because he will know that he has some abnormality of his blood pressure but he will not be told by me that he has "essential hypertension" or hypertensive disease.

There is one good reason why I use the classification "vascular hyperreactor" and avoid the term "essential hypertension" for that kind of person. As soon as you say "essential hypertension" to a patient, he thinks of all the worst things he has heard about it and will become unduly anxious about himself. Some or perhaps many people with a mild essential hypertension, a mild type of vascular reaction, will live for years and not have any complications of hypertensive vascular disease. That was a real problem for us during World War II when I used to see three or four young men a week who came to the clinic either because they had been turned down by the draft board or turned out of the service and were just told, "You have high blood pressure." Most of them were hyperreactors and some of them were only systolic hyperreactors. If they were systolic hyperreactors, I told them that I did not think it meant anything as far as the future development of serious high blood pressure was concerned. If they were diastolic hyperreactors, I told them that only by following them

along for several years could we tell about the significance of the abnormality of their blood pressure.

Some of these systolic hyperreactors might come back to you with the idea that I did not think it meant anything. Well, that is my own personal opinion. I think that person is insurable and that he should not be rated up on the basis of his systolic hypertension. I am, of course, assuming that the presence of some underlying systemic disease, such as hyperthyroidism or pheochromocytoma which might be causing his systolic hypertension, has been excluded. But I cannot tell you accurately about the insurability of a young person who has a blood pressure of 150/100. I cannot get over into your business, because I do not know enough about it, but my personal feeling is that, that person should not be denied insurance, if he is willing to pay something extra for the probability that he is not going to continue to be as good a risk as he is at the present time.

PRESIDENT WILLIS — We are certainly grateful to Dr. Hines for this splendid presentation and for the time he has given us. In the past, a number of doctors from the Mayo Clinic have appeared before this group. I was anxious to have an opinion from the Mayo Clinic on this subject, and I am very grateful to Dr. Hines for accepting our invitation. Thank you, sir.

The subject of the next paper is one in which many companies have been interested, and there may be a few that know how to handle it. The Lincoln National was a pioneer in substandard life insurance, and they have made great strides in that field. They are going into substandard accident and sickness insurance, and I am glad that we can have a paper on this subject from Dr. William H. Scoins, Chief Medical Director of the Lincoln National.

SUBSTANDARD ACCIDENT AND SICKNESS INSURANCE

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The extension of life insurance benefits to an ever increasing number and variety of impaired lives has long been a major aim of the life insurance industry in general. The success of this effort has been due largely to a readiness on the part of the companies to experiment with the acceptance of risks previously unclassified or considered to be unclassifiable.

Experimental technics along these lines were logical extensions of the numerical rating system and reflected the experience developed from more comprehensive mortality tables on both unimpaired and impaired lives. The decisions to apply such technics more frequently with increasing confidence was stimulated at least to some extent by modern medicine's improved diagnostic and therapeutic skills. Additional encouragement came from a public educated in the belief that physical and medical impairments are not necessarily inconsistent with normal life expectancy.

Whatever the initiating impulses, the end result of current underwriting methods on substandard risks has been to make life insurance available to as many people as possible at as fair and reasonable a price as is consistent with sound business principles. That, in the last analysis, is the primary aim of the industry. It is to the enduring credit of the life insurance companies that they have assumed this obligation voluntarily at their own risk and within the free competitive framework of American enterprise.

If universal coverage is the aim of life insurance, why then should the accident and sickness field be content with any lesser goal? The answer is that it should not. The accident and sickness insurers ought to fulfill their obligation to the public by offering their products universally to all, or nearly all, at premiums that are fairly and properly priced according to the degree of risk.

The volume of accident and sickness insurance now in force covering a very large number of individuals together with the benefits paid out each year is evidence of the remarkable progress already made by the industry. Nevertheless, some critics declare that accident and sickness protection still falls short of what the public needs, and that the industry alone may not be in a position to satisfy those needs. These criticisms are not valid as the companies offering accident and sickness contracts readily appreciate. The many excellent forms of coverage available could adequately meet the needs of most people if properly marketed. The industry continues the development of new contract plans to give still more medical and surgical protection. For example, the major medical expense contract is a recent effort to provide more comprehensive protection. If there is a deficiency in the industry, the underwriting methods might be the responsible factor in view of an adequate number and variety of plans available. Are the rules of underwriting so rigid that applications of a significant number of persons with adverse medical history or physical abnormalities are rejected wholly or in part? Is the industry willing to make available accident and sickness insurance to persons with any number and variety of impairments? Should present underwriting practice be reviewed to correct any possible unfairness and to explore avenues of progress?

Underwriting accident and sickness risks is largely a matter of judging impairments in the individual case. Proficiency is developed through experience and is augmented by basic knowledge of disease histories and residual static impairments. In this field, information from clinical sources is more extensively used than in life underwriting. The practical application of such knowledge determines the total risk by estimating the influence of the impairment on certain probabilities in terms of degree of severity, duration and cost. These probabilities include possible recurrence, later developments or complications and associated disability, effect on the general health of the insured and progression of the original impairment resulting in disability. There is also the probability of elective disability resulting in a claim for surgical benefits or illness characterized by subjective symptoms based on objective evidence of impairment in the history or physical examination.

If the estimate of probabilities exceeds the disability hazard usually present in the unimpaired life, the ultimate cost of future disability is controlled by exclusion riders, extending waiting periods or by a substitute plan. If the disability hazard is distinctly greater than that of the unimpaired risk, the application may not be acceptable, unless the hazard can be excluded by a rider.

Therefore, accident and sickness insurance is being underwritten as a substandard type of business on impaired applicants within the limits of the methods just described. They are not considered to be entirely satisfactory to our policyholders, prospective policyholders, the agency force or the underwriters. Certain types of exclusion riders might reflect upon the public relations of the company. Policies with vague statements excluding from coverage an area of the body or a body system are accepted with reluctance and suspicion. Similar modifications of the contract may become highly unsatisfactory when made a part of the renewal procedure following a legitimate claim. According to some underwriters, the exclusion rider may deter the presentation of claims while it fails to give the company the protection it needs and expects.

Symptoms and associated disability are characterized by their subjective implications rather than their objectivity as related to cause and effect. Underwriters, experienced in the practical development or application of riders to individual underwriting problems, realize the difficulty in clear and comprehensive definition within the desired scope. Furthermore, exclusions are not universally applicable. There are instances in which some approach, other than exclusion, is needed since the only alternative usually available is to decline acceptance. Finally, the effectiveness of riders is inherently limited because the method provides something less than full coverage at regular premiums. Since it cannot, therefore, cover all disabilities. it cannot achieve the goal of universal coverage.

Waiting periods offer certain mutual advantages to the company underwriter and the applicant. First day coverage for disability from illness and coverage for short intervals would defeat the real purpose of sickness insurance. An offer of a different plan adds flexibility and security to the underwriting procedure.

However, these modifications of contract may cause dissatisfaction, confusion and sales resistance, making it necessary to sell the applicant again. This situation discourages the successful life sales representatives from selling accident and sickness insurance because of their impression that it requires too much time and effort.

Although there are objections to the use of exclusion riders, waiting periods and plan variations, they make possible the means of assisting the public to meet the costs of medical and surgical illness and loss of income by a disabling accident or illness. Their continued use, however, will limit progress toward more universal coverage. Is there a method, or combination of methods, offering a solution to the problem? Underwriting the substandard life risk involves the principle of grading the degree of risk in terms of extra premiums for an expected increase in mortality. Is it possible to apply this procedure to accident and sickness insurance, and will it be practical? Will this be more acceptable than the modifications described and would it permit extension of coverage to risks previously considered unacceptable?

Actually, a part of the industry is now engaged in underwriting substandard disability insurance at standard premiums. Some companies include the waiver of premium feature for disability in contracts on all risks whose expected life mortality does not exceed 150 per cent. These include risks that are substandard for conditions normally associated with long periods of disability, for example, recurrence of pulmonary tuberculosis or psychoneurosis. May this not be considered a type of coverage for income replacement? Why not consider disability in its most comprehensive aspects and provide a technic for marketing the insurance accordingly.

When first considered, the idea appeared impossible because the concepts of indemnifying future disability involve underwriting factors which find no parallel in the experience with life insurance. The suggestion is not an original one. In 1951 Mr. Roy MacDonald presented to the industry an excellent basis for beginning such an experiment together with a clear and convincing exposition of his own philosophy on the subject. Disability may occur and recur, each period being unpredictable as

to time, duration, degree and cost. On the other hand, the life insurance contract is concerned with the time of death as the only unpredictable factor. When the life insurance contract is made, the cost has been predicted and established in advance. Presently, there are no data available on accident and sickness insurance that would form a basis for morbidity tables. On what basis could the extra premium be determined or the extra debit be added for a particular impairment or group of impairments? Secondly, the moral hazard known for its uncertainty in life insurance is far more difficult to evaluate and of considerably more importance in accident and sickness insurance. It is nearly impossible to convert this into debits of a numerical rating system. Finally, personal and widespread economic reverses have an adverse effect on the experience with accident and sickness insurance. The combination of one or more known impairments with some degree of moral and economic hazard presents an underwriting problem of considerable magnitude. These factors are of great importance and must be given serious consideration before contemplating substandard accident and sickness insurance.

Progress is achieved by accepting new ideas for careful and detailed examination and by being willing to experiment with them. It is apparent that the principle of charging an extra premium for individual impairments cannot be applied in this field as universally as it is in life insurance. There is no question about the philosophy that impairments such as coronary artery disease, mitral stenosis, aortic insufficiency, some types of arthritis, the psychoses and psychoneuroses present health and accident hazards too great for proper evaluation. Moreover, it would seem practicable to exclude from the contract other more specific impairments including hernia, some types of amputation, tonsil disease, nasoseptal defects and blindness than to attempt imposing an extra premium.

Most impairments, however, would fall between these two extremes and might be underwritten either on the extra premium basis alone or in combination with an appropriate exclusion rider. For example, benign essential hypertension might be accepted within certain limits on the extra premium basis alone. The known hazards of this condition are such as to exclude satisfactory underwriting on a rider. These hazards are relatively slow in

development and appear late in the premium-paying period of most contracts. They may be catastrophic in nature, causing sudden death in a fair number of cases and prolonging disability in an equal number of others. A single maximum claim, in all likelihood near the end of the premium-paying period, may be considered probable.

Why should the history of bronchial asthma always call for an exclusion rider? A waiting period of one or two weeks would seem more than ample for the attack of asthma depending upon the degree of severity and possible complications. But, would not an extra premium from a group of such cases adequately cover the risk of an occasional severe case as well as those which later develop various complications? The extra premium approach, of course, may not apply to all cases of asthma or benign hypertension, especially those known to be severe or complicated.

Some impairments are characterized by hazards of heterogenous type. Diabetes mellitus as a disease syndrome is an excellent example. Disability and death result not from the disease, but from its many and usually serious complications. Under proper medical supervision, the patient can do much in the matter of preventing development of these. Great care must be exercised in underwriting persons with diabetes for accident and sickness insurance. Acceptance on some adequate basis would encourage people with diabetes to observe more closely the principles of good care and thus continue to qualify for the needed insurance coverage. Persons with diabetes are a large source of prospective policyholders. Their favorable attitude toward the management of the disease, excellent work and attendance records now possible among diabetic individuals, is encouraging.

Some impairments may possibly require both an exclusion rider and an extra premium. Among this group are those with the silent gallstone, recent history of cholecystitis without operation and with or without stones, silent kidney stone without obstruction and peptic ulcer with operation. The hazards of surgery in these varied conditions and the possibility of recurrence are best covered by an exclusion rider. In addition, an extra premium may be needed if there are problems of differential diagnosis, secondary effects occurring as complications in the body system concerned

and the possibility of an adverse influence on the general health of the individual.

The considerations just outlined are a statement of basic philosophy in its simplest terms and may not encounter serious opposition. Their application to the individual impairment would be qualified by the underwriter's knowledge of the impairment in question, the interval of time elapsing since recovery, the quality and effectiveness of therapy and the ability demonstrated by the individual to handle the problem. If the extra premium is the method of choice, the original underwriting would be important because medical examinations and statements from attending physicians would be a part of the required data more frequently than at the present time. The problem of greatest importance, of course, would be the establishment of a method or means of determining the amount of extra premium necessary. How would the relative value of any impairment class be expressed? This concerns not only the principle that some diseases by their natural history could be covered by the extra premium but also the approximate relative costs of medical, surgical and hospital care in the event of disability.

Experience in substandard life insurance is the only source of data related to this problem. Since there are no basic morbidity tables or experience data from which to make a beginning, it seems reasonable to investigate the relationship, if any, between morbidity and mortality rates. Considerable data now available accurately reflect the mortality ratios expected from a number of various impairments. It seems reasonable to expect an impairment with a mortality ratio above 100 per cent of the standard to be associated also with an increased morbidity ratio. If the standard accident and sickness risk morbidity ratio were assessed at 100 per cent, could there be added (in percentage) for a proportionate increase in the morbidity risk, some multiple of extra debits such as is now the custom in substandard life insurance? What that multiple should be remains to be determined. However, the principle of relating morbidity to mortality in this manner seems to be a sound one. This would require the application of good judgment, a careful estimate of the disability potential of the impairment and the probable nature of the cost for medical, surgical

and hospital care as well as loss of time incurred. The cost of underwriting impairments with an extra debit will vary according to the probable nature, degree and duration of anticipated disability because these will necessarily influence the probable method of treatment, the likelihood of surgical interference and of hospital, institutional or domiciliary care. At least some estimate of relative costs can be determined by these probabilities.

Some impairments, such as arrested pulmonary tuberculosis, present a small but very definite probability of recurrence. If it does recur, there may be an extended period of time loss and treatment even extending through the maximum benefit period of the policy. This type of risk, and others with similar disability hazards, is best handled under current methods of underwriting by an exclusion rider. This is based on the provision that the impairment can be described adequately and precisely. Individually, the cost factor would be significant. However, in groups, this significance would be less and would be absorbed in an extra premium applied to all cases in the class. This would be a desirable step toward universal coverage.

Other impairments such as hay fever and asthma are associated with a high probability of recurrence, with short periods of disability but with little risk of significant hospitalization, surgical treatment or time lost. Under these circumstances, the anticipated cost hazard to the individual is light and the use in underwriting of waiting periods, elimination riders or both are adequate. In some impairments the hazard of future disability is not one of recurrence but rather one of complications or adverse effects on the general health. Obesity and hypertension are good examples, and obviously if acceptable, they should be underwritten on an extra premium basis. Until correctly determined by experience, the relative cost increment of the extra debit should assume a significant place in the overall calculations.

Of course, there are a number of impairments such as chronic organic valvular heart disease, coronary artery disease, degenerative types of arthritis and impairments of the central nervous system in which the probability of progression is not only high, but future disability is likely to be prolonged and expensive. The cost factor is so high in these that it is considered outside the

anticipated limits of experimental substandard underwriting.

In the establishment of any substandard debit the type of coverage as well as the nature of the impairment and relative costs of future disability must be considered. The premium increase for loss of time coverage resulting from accident will frequently differ from that for loss of time resulting from sickness. This is demonstrated in present underwriting methods where many cases are accepted for loss of time coverage resulting from accident and at the same time rejected for loss of time coverage from sickness. This does not imply that accident coverage can always be issued at standard premium rates. Many impairments are associated with an increase in the accident hazard by increasing the probability of accident occurrence (blindness in one eye is a case in point), or by adversely affecting the anticipated recovery period from an accident occurring independently of the impairment.

Hospital coverage also differs from loss of time coverage because the character of some impairments is associated with a significant increase in the hazard of hospitalization and medical care. In addition, the inability to use the extended waiting period method with hospitalization coverage frequently requires that the two types of coverage be treated differently.

Time and experience will tell whether this scheme of extra premium charges for substandard accident and sickness insurance is practicable. At this stage, the concepts outlined are purely philosophical and when put into practice they must be applied as an experiment in underwriting.

An extremely conservative approach to the problem has been suggested, limiting exposure to selected impairments and later extending it to others as warranted by experience. However, to accomplish this would require an extremely long period of time for the accumulation of data and might prevent a sufficiently broad spread of risk. It was indicated that the substandard extra premium approach alone could not be universally applied and that it would seem better to combine it with present methods. The Lincoln National, therefore, proposes to enter the field on a broad, general basis, integrating the substandard idea with present methods. It is hoped this will result in a flexible system

allowing it to meet problems as they arise, changing, if necessary, in conformity with experience while at the same time affording a broad spread of risk. Equally important in such an experiment is the option of enlarging the number and variety of acceptable impairments and thus, contribute to the industry's progress toward universal coverage.

PRESIDENT WILLIS — Are there any questions? There must be some who are going into this field, who would like to ask Dr. Scoins something about it.

DR. DONALD E. YOCHEM — I would like to ask a question. Dr. Scoins, do you propose, then, to apply both the waiting period and the numerical rating and the waiver or rider, all three, to each individual who is substandard?

DR. SCOINS — It depends largely on the type of impairment. If the waiting period will take care of it, we will exercise that right, at least on occasion. Some will have both an extension of the waiting period with a slightly increased premium and, as indicated in the paper, some of them we necessarily exclude by rider because of the associated effect that may be had on the general physiology. We are dealing with descriptive terminology by doctors, and a rider is just an attempt on our part to get away from assuming responsibility. But let a doctor come in and give a different terminology to the diagnosis and it is worthless. Therefore, in developing this, we must try to do a good job for two parties: first, our policyholder, and then the company. There should be a little profitmaking, too, but that may take time.

DR. DAVID L. SELBY — Dr. Scoins probably had a good reason for not mentioning the question of deductibility allowances. I have been considering it and wonder if he would give us his reasons for not saying anything about deductibility in such things as bronchial asthma.

DR. SCOINS — If I understand your question correctly, you mean the deductibility on some specific impairment?

DR. SELBY — Yes, such as bronchial asthma.

DR. SCOINS — Rather than the exclusion rider?

DR. SELBY — Yes, rather than the exclusion rider, where there are many slight attacks and where a $25 deductible sum would cover a great deal.

DR. SCOINS — Well, that, in another way, is taken care of by the increased waiting period, is it not?

DR. SELBY — Yes, but just a straight deductible sum. You did not mention it at all, and, I am sure, for a very good reason.

DR. SCOINS — I think the best reason is that I did not even think of it. But the deductible sum is a subject which has to be given a lot of consideration, because there has to be a coinsurance feature. I did mention that we cannot have first-day coverages. I think there has to be a bilateral interest. Any time we start handing a blank check to anyone, I am afraid we are getting away from all insurance principles.

DR. JOHN E. BOLAND — I would like to know whether you are going to use present substandard underwriting tables in an attempt to make an appraisal on your substandard health and accident.

DR. SCOINS — We have no substandard tables on morbidity. We have substandard tables on mortality. We believe that there is a relation between mortality and morbidity. Our attempt to substandardize will be in a similar direction. Now, what the cost will be, I do not know. That is being developed. But it will be on the same basis, or approaching the same basis.

DR. F. TULLEY HALLAM — Would it be possible to develop a rider which is modifying rather than excluding? At present, if we apply a rider, in effect, we make it a standard risk for all other conditions and exclude liability for certain specified risks. Would one approach for substandard Accident and Sickness issues be to limit the liability, in other words on a prorated basis? We would apply a rider that in the event of loss of time, disability or hospitalization, we would grant 20, 50 or 75 per cent coverage. Would that be an approach? Could we get a rider such as that through the insurance departments?

DR. SCOINS — I do not know whether we could or could not, but it is an approach. I am opposed to endorsements and always have been, and I still think that the primary value of endorsements is to deter the presentation of the claim, rather than the

protection they may afford. But we are just dealing in semantics, as you see.

Another problem in connection with endorsements is that if one is applied to gallbladder disease, for example, there may be associated physiological complications associated with the etiological factor of the gallbladder. The doctor can change the diagnosis and we do not obtain any protection.

I assume that your suggestion has been given a lot of thought. Whether or not that would be more acceptable to the public and better for the insurance companies, I do not know.

DR. A. E. PARKS — I wonder if Dr. Scoins would say a few words about the substandard applicant for group sickness and accident, where you have a late entrant who wants to get into a group.

DR. SCOINS — Are you asking me how we deal with them?

DR. PARKS — That is right.

DR. SCOINS — Just as you deal with them. When the "come latelies" are slowly making up their minds, we like to have them qualified just like an individual applicant on group business.

DR. H. L. HAUGE — You said that you proposed to approach this on a broad scale and more or less give it, if you do offer substandard, for all impairments, as a combination of substandard and waiver. Did I understand you correctly to say, then, that you would have just one policy where the proposed insured would not be able to elect? If, for example, he had asthma, he would not be able to elect to take a policy that had an exclusion rider, or, if you had a substandard policy, would he have to take one or the other? Would you have one or the other for all your impairments?

DR. SCOINS — Yes, we will do the underwriting rather than the applicant.

DR. HAUGE — You will decide whether he is going to have a rider or substandard policy?

DR. SCOINS — Yes, or both.

DR. HAUGE — He would have no choice in the matter?

DR. SCOINS — No. But we are not going to try to select the impairments, to begin with, other than, as you mentioned, we will try to go into the substandard business and get a spread of risk.

PRESIDENT WILLIS — Thank you, Dr. Scoins. Your paper has been most helpful and I am sure that many members of this group will be glad to use your suggestions.

Prior to about ten years ago, a history of liver disease was seldom seen among applicants for insurance. Today, such a history is not uncommon, and the problem of classifying these risks is difficult. The next speaker is recognized as a leading authority on liver disease. His subject is, "The Clinical Evaluation of the Commoner Hepatic Disorders." Dr. Franklin M. Hanger is Professor of Medicine, College of Physicians and Surgeons, Columbia University, and attending physician at the Presbyterian Hospital in New York.

THE CLINICAL EVALUATION OF THE COMMONER HEPATIC DISORDERS

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The impact of the new viruses which are now known to attack the liver, the new industrial hazards constantly being invented, and even the new pharmaceutical preparations on the market have all contributed toward changing concepts of etiology and physiologic processes in this complex organ in both its normal and diseased states. Disease of the liver was simplest when we did not have laboratory tests, when we were all optimistic, and when we guessed. Now we are beset by a group of competing laboratory tests, and it is their interpretation and their misinterpretation which doubtless plagues each of you.

Is disease of the liver present? That is the important question. The most convenient criterion is either hepatomegaly or jaundice. Others suggesting liver disease include ascites, vomiting of blood, the appearance of collateral circulation in the esophagus or on the abdomen, the appearance or development of spider angiomata on the face or upper extremities, splenomegaly, pigmentation suggesting hemochromatosis, or, rarely, mental and physical discoordination associated with a large liver. Nose bleeds and hemorrhagic tendencies are less significant and even though macrocytic anemia is not due to liver disease, the question may arise with this type of blood disorder.

When the liver is diseased the cause is of first concern. Second, is it associated with a deficiency in the functioning liver mass? If so, is this deficiency permanent or temporary? Another and most important factor is whether or not the process is an irreversible one.

I should like to discuss a philosophic aspect of laboratory tests. Anatomic dissections of the liver indicate that in spite of its

large size, the functioning unit is really a single layer of parenchymal cells. These are separated by an endothelial cell, known as the Kupffer cell, from the blood on one side and the biliary capillary on the other. All functions of the liver represent communications with these outside areas; in other words, each liver cell has two functioning surfaces. The liver either manufactures substances and excretes them into the bile, or removes substances from the blood and excretes them into the bile. These, then, represent the excretory function of the liver. The excretion of water and cholesterol appear to be a regulated function of the liver with about 98 per cent of bile being water. We know that the bile salts probably are the only useful constituent of the bile, and they are important in the emulsification of fats in the intestine. They are manufactured by the liver, by the same process perhaps that cholesterol is synthesized and excreted in the bile. Also many of the active steroids from the adrenals and the gonads are conjugated into soluble products and excreted in the bile. And then, of course, there is bilirubin, that very valuable telltale pigment, extracted from the blood and once more excreted in the bile.

A test of the excretory function of the liver does not depend on this or that cell but rather upon the overall mass of cells. However, there comes a time, if more and more of these cells are sick and lose their dynamic vigor as it were, when this excretory function becomes impaired and the secretion of bile is impaired. Then the patient will develop jaundice. In other words, a diffuse disease of the liver could affect this excretory function and hepatitis is such a disease where sometimes many cells or sometimes only a few are injured, but some may even die.

In addition to these excretory functions the liver has ready access to the blood. Each liver cell is in contact with a capillary and some of the substances manufactured by the liver, such as urea, uric acid, conjugated benzoic acid—the basis of the hippuric acid test, pass into the blood and out of the body by way of the kidneys.

More important still, from the point of view of the liver as a functioning organ, is its transformation of practically every foodstuff. Amino acids and proteins can go into the liver there

to be turned into other proteins. When the body needs them they emerge into the blood stream again. The same is true of glucose going into the liver to be stored as glycogen, then, when glucose is needed glycogen breaks down to supply it and maintain the blood sugar level. This is true also of fats. We regard fat as a rather permanent adornment and so it seems to be in some persons. In the liver there is storage of fat at all times and that fat is in dynamic equilibrium with the needs of the body. The liver can take on fat very readily and in health it can discharge fat. There will be another reference to that in connection with the alcohol problem.

There are at least five hundred known functions of the liver and in a few more years there will probably be twice that number. Practically all these functions depend upon one or more enzymes and often very complicated enzyme systems, some of which are seen in textbooks, with arrows running every which way. Which way these arrows will move depends not only on the diet but also on toxic agents. It depends on the health of the individual liver cell. Sometimes the liver cell may lose one particular enzyme. For example, if one individual receives a therapeutic dose of dicumarol the effect of that drug would impair the manufacture and secretion of prothrombin. If one should look at the liver of that person with a microscope, no histologic change would be detectable. Many of these derangements of the liver cannot be detected as they are part of the complicated system of internal metabolism.

In other words, our liver function tests are rather crude. In the first place, when we examine the blood or conduct a test on the blood as a so-called liver function test, it should be remembered this represents an equilibrium of the movement of a combination of forces to be regarded as a unit. When the liver becomes impaired this equilibrium shifts. For instance, as the liver mass decreases the serum albumin maintained in the blood is at a lower level. It does not mean that albumin is not being formed; it merely means that the overall balance is towards a lower level of blood albumin. And so it is with many other functions of this complex organ. Note, too, how various toxins, various viruses, and very

important, a decrease in oxygen or blood supply, can affect this overall equilibrium.

With that as a background of the dynamics of liver function we will go very rapidly over some of the conventional tests which, I am glad to say, are in ever wider use so that doctors at the present time at least can speak the same language when referring to them. Unfortunately, the tests are not standardized and therefore laboratories change in their variations of normal. In spite of this we are approaching little by little more sensible concepts.

I should like to emphasize the bilirubin problem. Whenever we have a prompt, direct-reacting van den Bergh, we can infer that there is derangement of the liver or of the biliary tree. It always indicates disease. It is important to realize that because some people are congenitally jaundiced the liver does not maintain the usual physiologic level of bilirubin in the blood. When we examine these people the van den Bergh reaction is usually of the indirect type.

Bromsulfalein excretion is a most important test. It is not specific, depending on the overall function liver mass rather than on a definite number of liver cells. Likewise, if some noxious agent affects the functional vigor of the liver cell or if the blood supply to the liver is shunted around the liver, impairment of excretion results. But, at any rate, bromsulfalein has considerable value. The problem is, how much to give the patient? It is given on the basis of body weight and the potential errors of that method are well known. Some people may receive too large a load and some too small a load in terms of its clearance. I do not believe that one bromsulfalein test is adequate, because almost any intercurrent episode, such as an infection or bout of fever, may affect it.

The test which has great clinical significance is the serum alkaline phosphatase of the blood. It is elevated in early hepatitis and in most cases of obstructive jaundice. The mechanism of this important change is unknown. It does not parallel the serum bilirubin in patients with partial obstruction to the biliary tree and the elevated alkaline phosphatase may be the only abnormality found. However, it is of no value when there is overt disease of the bone. We also know that for diagnosis of tumor or any expanding lesion of the liver, sometimes the alkaline phosphatase

level is the only clue. There is evidence to indicate that the maintenance of the alkaline phosphatase level in the blood is through a different mechanism from that by which the serum bilirubin level is maintained. Therefore, the alkaline phosphatase is often an extremely important criterion, particularly when used in combination with the serum bilirubin.

Total serum cholesterol can be affected by so many things besides the liver that it is mentioned with some hesitation. Some of these metabolic functions have been mentioned and it must be emphasized again that they are extremely crude and often when they show impairment the damage to the liver is great. I feel that the value of all these tests is primarily in their repetition. When we repeat any liver function test, we must be sure to have our patient under the same basal conditions. If the first one is done with the patient in bed, the second should be done with the patient in bed. If one is done with the patient on a certain diet, repeat it with the patient on the same diet because all these tests can be affected extraneously, and not necessarily by the status of the liver itself.

Today the hippuric acid test is not done frequently. It is too complicated and too subject to error. The urinary urobilinogen test is a valuable crude screening test. But, to use it as a quantitive test we would have to know what was happening to the blood cells, how much hemoglobin the patient had in his body, and the amount of urobilinogen excreted in the stools. It is at best an indication of liver disease, but it may also be an indication of hemolysis. The galactose tolerance test, once again, is very crude and is not generally used. The serum cholesterol ester is probably one of the best of the available liver function tests. There is some evidence that patients exposed to carbon tetrachloride or other chlorinated hydrocarbons may show some reduction in the esterifying powers of the liver before there is any other detectable change. I have not been able to confirm this in all cases. However, if one individual in a group exposed to carbon tetrachloride should develop a progressive reduction in the cholesterol esters of the blood, particularly if associated with some other changes such as enlarging liver, that individual has demonstrated a susceptibility to that hazard. The

plasma prothrombin time is of no value as a screening test. When that becomes deranged the liver is usually massively destroyed.

Another function of the liver which is of great help in evaluating its functional status is its ability to make proteins. There are some constituents of the protein, particularly some of the lipoproteins, that have a half-life of only a few hours. The serum albumin, as measured by conventional methods, has a half-life of about 15 days. The serum albumin, as far as we know, is made exclusively in the liver and as the functioning liver mass diminishes, by destruction of liver cells, fatty degeneration, or by tumor replacement—while it is nonspecific—there is the reduction of serum albumin as evidence of liver disease. It simply indicates a decreasing functioning liver mass. The serum globulin also is of great importance, because about one-third of the liver consists of mesenchyme or connective tissue, a very specialized reticuloendothelial tissue. When this tissue becomes inflamed as a primary condition or in association with parenchymal degeneration the serum globulins tend to rise. Some of these globulins are so specific that they can be detected by special tests. This represents a derangement of the serum complex, particularly among those labile lipoproteins in the albumin and the alpha globulin fraction, which can change very quickly. When they become deranged the test becomes positive. The positive cephalin flocculation, as we will see in just a moment, also can be caused by abnormal globulins. The thymol turbidity is an extremely valuable test, and it indicates abnormalities in the globulin fraction, primarily in the gamma globulin group. Unfortunately, inflammations throughout the body as well as of the liver may give a positive thymol turbidity, because of these increased globulins. After hepatitis, for instance, we may have a positive thymol turbidity lasting for weeks and months and even years, similar to a positive Widal which depends on a globulin.

Two mechanisms can cause a positive cephalin flocculation and this is emphasized because it is a constant concern. The patient who never had liver disease may have a strongly positive cephalin flocculation. Some years ago we took normal sera and also sera from patients with hepatitis, separated these into fractions electro-

phorectically and found that if one adds normal albumin fraction—and this includes the lipoproteins—to hepatitis gamma globulin, one could make a negative test, as on normal serum. On the other hand, these labile fractions in the albumin added to normal gamma globulin, gave a positive test. That is the mechanism of the positive test in hepatitis — a loss of the stabilizing factors in the serum complex. The test is done on a lipid emulsion and these labile lipoproteins prevent the gamma globulin in human blood from giving a positive test. When we began working with experimental animals it was discovered that a normal dog always had a positive cephalin flocculation. Dog gamma globulin gives a positive cephalin flocculation test even when human albumin is added. On that basis the dog gamma globulin is different. In fact, only the monkey and the human have this property of the gamma globulin being stabilized or neutralized, as it were, in this complex reaction by these stabilizing forces. Then it was learned that in certain diseases people simulated the dog. These "human canines" are persons with infectious mononucleosis, queer diseases of the spleen, hemolytic anemia, some of the unusual bone marrow diseases as well as several others. In other words, it is possible to get a positive cephalin flocculation in some people who apparently are in perfectly good health, where it is not due to liver disease at all.

Some of these people have been followed for many years, and they are somewhat like the people who have a congenitally positive Wassermann reaction. It may run in families. We have been rather surprised in following some of those who had an unexplained positive cephalin flocculation to see how many of them eventually developed lupus erythematosus, hemolytic anemia, or disarrangements of the reticuloendothelial system. I would not necessarily draw a final conclusion about a person because of a persistently positive test — not a temporarily positive test — even for a year or two. These people who have a positive cephalin flocculation do have a derangement of the serum complex. In the absence of liver disease, it does represent an abnormal globulin which may be the precursor of some of these obscure systemic diseases.

First among the two diseases which beset us most at the present

time is hepatitis. Literally millions of Americans have had hepatitis, and it continues to be one of our great health menaces. As we know, the hepatitis virus can affect the parenchymal cells, sometimes one and sometimes the whole lobule. At other times, it seems to focus on the reticuloendothelial elements primarily. Sometimes it is in the form of the so-called cholangiolitic hepatitis in which there is an intense sterile inflammation in the portal triads often extending into the Kupffer system.

The findings in hepatic function tests during hepatitis depend to a degree on the area of hepatic tissue involved in the disease process. When hepatitis affects the parenchymal cells we get a positive flocculation and often there is jaundice. There may be elevation of alkaline phosphatase at the beginning. If the disease affects primarily the interstitial structures, as represented by the portal triads, then there is evidence of obstructive jaundice and the patient may itch and have all the features of obstructive jaundice. Fortunately, these cases are few but they present a problem in differential diagnosis.

In advanced cases of hepatitis there is great necrosis of most of the liver cells. The only ones that are even semiviable are those around the portal triad. This is mentioned only to indicate that a patient of this type would have a very high cephalin flocculation and a very long convalescence. But the repair of the liver in most cases of acute hepatitis is remarkable and as long as there are a few nest eggs, as it were, these cells proliferate and restore the completely normal architecture of the organ. It takes time. These people are often quite ill but once they recover their laboratory tests will return to normal. Occasionally, when the destructive process is even more massive and every liver cell is depleted, then the lobules cannot regenerate. In that case there is a collapse of stroma which can result in a nodule of the liver but from all challenges that we can put on the liver, it is essentially normal. So, then, the tendency in hepatitis is to get well and that is why I regard most of these cases with great optimism.

Now, let us consider a case of hepatitis with massive destruction of liver cells. The other type mentioned was primarily a disease of the portal triads but in the more serious types there is swelling and obstruction or compression of the smaller bile ducts

and compression on the portal vein. There may be a temporary disturbance of blood supply to the parenchyma. But, this is primarily an obstructive process. Bile plugs form in the parenchyma just as in any other obstructive jaundice.

Since the wide use of thorazine the incidence of what appears to be obstructive jaundice has increased. These patients — and it occurs in one to three per cent of patients on thorazine — develop just that, an endematous cellular infiltration of the portal triads. Apparently, most thorazine patients recover. Now and then an unwily surgeon makes a diagnosis of obstructive jaundice because there is an elevation of alkaline phosphatase and a negative flocculation test. In other words, there is an interhepatic obstructive process. The fact that people handling the drug get dermatitis very readily would suggest that the drug is excreted by the liver cells, and that the process is something comparable to contact dermatitis of the biliary tree. It behaves like it. After weeks and months, usually there is spontaneous recovery. An interesting feature is that many of these people after going through this episode of drug sensitivity can take the drug without any further discomfort. The eventual effects are not yet known. As far as I know, none of them has yet developed a permanent scarring process known as biliary cirrhosis. In other words, the outlook is good but the thorazine jaundice, and some caused by virus, are quite similar when they affect the interstitial structures.

The great problem, certainly the problem which comes to me more frequently, is that of a person who has had hepatitis and things are not quite right. The doctor in charge is often disturbed. Is this patient going into one of these irreversible interstitial deforming lesions, ending of course in biliary cirrhosis? We have mentioned that very severe hepatitis can leave scars on the liver just as smallpox can cause disfigurement of the skin. But, they are of very little clinical significance.

When we suspect chronic disease — and this is in a very small number, certainly less than one percent of all the patients with hepatitis — there are some things regarded as having ominous importance. Once this process develops, concern increases because chronic hepatitis is usually progressive although two or

three patients have been observed for two or three years with progressive symptoms and then have reverted back to normal.

Among the things that are very important in chronic inflammatory disease of the liver is, of course, the character of the liver itself. The liver gets larger and it often remains tender but most important of all is its consistency. A cirrhotic liver is a hard liver and when it becomes firm because of the increase in connective tissue this is of great clinical importance.

In the presence of jaundice an indirect van den Bergh following hepatitis has no significance, in my opinion. When the van den Bergh is direct, or when people have little episodes of jaundice with bile in the urine, we begin to suspect an active inflammatory process in the liver. The development of a persistently palpable spleen or the appearance of fresh spider angiomata in the convalescence stage of hepatitis are unfavorable signs.

The persisting positive cephalin flocculation has to be evaluated. Many patients with chronic hepatitis, particularly those with severe degrees of the disease and those requiring long convalescence, may have positive cephalin flocculation and thymol turbidity tests lasting for months and even a year or two. Some of these people have symptoms. They complain of fatiguability and pain in the liver. Biopsy indicates that there are focal areas of inflammation in and around the portal triad. Some of these patients, if put to bed for a few days, will have a negative repeat test.

How do we handle those? Their management includes activity within tolerance and regulation of their lives so that they can be useful within their capacities, and on this most of them tend to improve.

The significance of hyperglobulinemia is obvious. In chronic inflammation of the liver involving these interstitial structures the globulins are going to be increased. Physicians become worried about this type of patient in convalescence from hepatitis. We keep asking, "What is the serum globulin?" I have never seen a patient with progressive chronic hepatitis who did not have hyperglobulinemia. Of course, in the advanced stage the serum albumin drops for reasons we have mentioned.

It is apparent that the diagnosis of hepatitis may be very diffi-

cult. Sometimes, the patient also has gallstones and we wonder about cholangitis. Sometimes, he is in the age group that may have cancer. The fallibility of our various tests makes it impossible to tell what we are dealing with on some occasions. There, we simply have to keep the patient under basal conditions and watch the course of certain tests. I have found it extremely useful to follow the course of the alkaline phosphatase and the serum bilirubin. In acute hepatitis, often even before the jaundice appears, the serum alkaline phosphatase may be quite high but the trend is downward and even while the serum bilirubin is rising the serum alkaline phosphatase is highest at the beginning of hepatitis. The serum bilirubin in hepatitis usually reaches its peak within a week or ten days and may stay up for an indefinite length of time then slowly decline.

When the patient has obstructive jaundice, tumor, cholangitis or stone, particularly stone in the common duct, the trend is for the serum alkaline phosphatase to keep rising during the course of the disease and often the serum bilirubin parallels it.

In tumor of the liver with enlargement we know that it is quite ominous to find an elevated alkaline phosphatase with, perhaps, no other disturbance. These expanding lesions often manifest themselves by serum alkaline phosphatase of 8 to 10 units, followed by the bilirubin and only late in the course may the patient be jaundiced. This, of course, is very schematic but it is amazing how frequently those two courses have helped in observing the trend of the disease.

Cirrhosis is a process of liver cell death and regeneration. Liver cells can die from the effect of many noxious agents and some of those which are known are anoxia, from any cause, carbon tetrachloride, phosphorus, other chemicals and viral infections, and occasionally amebiasis or certain bacterial infections causing necrosis. There is some evidence that in people on low serum protein diets for prolonged periods of time, the biologic vigor of these cells becomes impaired, so that some minor ailment may cause rapid deterioration.

Certainly, the cells of the alcoholic person lose their vigor and by "vigor" is meant not only the metabolic functions but also the

actual ability to live. As the unfortunate person begins imbibing alcohol there is an accumulation of fat in his liver cells. The livers of some alcoholic individuals are not affected by this metabolic defect, but to others alcohol is a toxin. This is reversible at first. Often there is only an enlarged rubbery liver at that time. An accumulation of fat is an indication of a metabolic shift in that patient's liver cells which eventually affects the viability of that cell.

These fat droplets become larger and in the advanced stage the nucleus is off at one corner while this fat practically fills the cell. This cell, then, has lost its vigor. Slight trauma will cause its death. And, moreover, when these cells die the surrounding cells lose the procreative urge and they will not multiply and maintain the lobule. Further, these cells undergoing acute death liberate irritating substances which stimulate the mesenchyme, the connective tissue of the liver. Following this comes cellular infiltrates, increase in fibroblasts, positive cephalin flocculation, and as these advance the patient develops hyperglobulinemia.

This, then, is the evolution of so many diseases, where the primary factor is what I like to call just cytoplasmic vigor. I do not know a better word because we do not know all the factors that affect it. Some people are born with this weakness, weak protoplasm, so to speak, in their liver cells.

I would like to emphasize that certain fatal types of liver disorders do not give rise to many liver cell derangements until the whole liver mass may be destroyed. Certain patients with chronic anoxia and some with chronic poisonings, for example, chronic carbon tetrachloride poisoning or other industrial poisonings, get red hyaline degeneration of cells. They are probably dead in that their function is lost but they do not undergo necrosis nor create much of a disturbance in the surrounding structures. The same is true when a tumor is pressing this cell out of existence. In this group the cells sometimes get so full of fat that they die and yet nothing marks their passing. It is merely a fat globule that is dying. They, too, do not create any great disturbance in the cellular proliferation in the liver. This group is presented as a warning because these fatty cirrhotic cases, particularly the alcoholic ones, can be very deceptive. They will have fever,

their livers are large, they may be jaundiced, and they are desperately ill. The prognosis is bad. And, yet, liver function tests may be quite deceptive in this group.

Then, we come to the cirrhotic patient who cannot be cured and the following histologic picture is to be emphasized. The fat can still be seen in the liver but surrounding it is a dense shelf of connective tissue. This shelf of connective tissue not only prevents a group of cells from joining its brothers but it also segregates the liver into many little livers, literally thousands, each nodule being a liver in itself. More than that, the blood supply that is so beautifully arranged in the normal liver is destroyed and these groups of cells get their oxygen from small blood vessels that creep in from the side. They will grow as long as there is oxygen to grow on. But note that any unfavorable effect — a little shock, a little hemorrhage, a little overexertion, an intercurrent infection—will cause these cells to lose their blood supply and undergo necrosis, causing more inflammation in the surrounding structures. Not only is that true, but in the connective tissue there are shunts. A great deal of blood in these cirrhotic cases goes into the liver, passes through the shunts into the hepatic veins, and emerges from the liver without ever having any contact with the liver cells. Therefore they have this very unstable blood supply, anoxia, with liver death going on at all times with a constant inflammatory response, this being the irreversible stage. In spite of the best medical care these people do not get well and the gravity of progressive cirrhosis is well known.

In cirrhotic patients the most important thing that we want to know is whether this process is continuing. Is it still active? Are cells still dying? Is there inflammatory response? The cephalin flocculation is very valuable in that regard. In a group of 17 patients studied while resting in bed, with diet, vitamins and all the adjuncts, we were not able to change the cephalin flocculation. Twelve of the 17 patients died within six months and the others have subsequently succumbed. Some of them can be nursed back by abstinence, proper diet, good nursing, and a certain number of those having strong flocculation reactions become negative. Many of those have done well. Many have gone back to

their original habitual weaknesses and have joined the deceased group.

The favorable outlook for those who have cirrhosis but in whom there is no evidence of activity is quite obvious. The chief hazard in this group, the inactive cirrhotic type, is portal hypertension and bleeding. This does not imply that a man with a cirrhotic liver, inactive cirrhosis, is a good risk because hepatoma can arise in these cases. There is wear and tear, their livers do wear out more quickly and the tendency to bleed from varices is still there. Nevertheless, these people stand minor adversity quite well and modern surgery benefits some. We have followed some of these patients for twenty and thirty years and they are still going strong. This is a group of interest to all—this question of fibrosis. It has mechanical liabilities but we have to evaluate it further to be fair to the individual patient and to properly manage that patient. This is a type of liver disease that, once recognized, one would not like to have included among life insurance policyholders.

We know that the liver is very vulnerable to metastatic disease. It shows several things. In the first place large tumors of the liver are seen where every liver function test is normal.

In hepatic tumors what happens to the bile duct drainage? Bile is simply regurgitated into the blood stream. It goes around through the general circulation, is once more delivered through the portal vessels and as long as part of the liver is healthy, bile is excreted in the normal way. The same is true with alkaline phosphatase although we know that as the tumor grows the alkaline phosphatase may show the defect earlier than any other constituent. In contrast to this tumor, one near the porta hepatis pressing on the bile duct, on the portal vein, on the hepatic artery, or on the lymphatics draining the liver, can give all the picture of hepatitis and many a patient has had an erroneous diagnosis made. The patient gets jaundice, has a positive cephalin flocculation test and it is only in the late stage that the true diagnosis may be made. We must always be very suspicious of patients with hepatitis who are not following the rules. They are the ones who probably should be explored surgically more quickly than those who follow

rules because we do not like to explore the hepatitis patient, obviously.

Now, what is the implication of all this? I think it is, very simply, that we have made strides in the evaluation of liver disease, particularly if we know what these tests mean and if we follow our old medical training. One feel of the liver is worth any of these liver function tests. But, if we integrate them and know their significance and, above all, know the dynamics of disease which can affect the liver, I believe we can evaluate many of these problems accurately.

DR. JOHN S. PEARSON — Dr. Hanger, you did not mention the medical liver biopsy. I was wondering what you think of that as a diagnostic procedure.

DR. HANGER — I think the medical biopsy, in skilled hands, can be extremely valuable. We can miss focal tumors and it is not without risks when we are dealing with obstructive jaundice. Since most obstructive jaundice is surgical, I feel that probably a laparotomy is the best way of investigating well-defined obstructive jaundice. Obviously, if the patient has been given thorazine observation must be delayed for some time, because it is probably jaundice from thorazine—just to make it harder.

One of the times when I think liver biopsy is most helpful is in the detection of the fatty liver. If you know that an alcoholic patient has a fatty liver, perhaps with a few strands of connective tissue, one can be much more realistic in handling it. That is a difficult problem and I have had very bad results indeed, even in treating these people at the early stage. Some who drink wines, the casual wine drinkers, are a particularly vulnerable group. When they are told that it is injurious they can easily stop and the processes have reverted back to normal.

PRESIDENT WILLIS — You spoke of wine. What about whiskey, Dr. Hanger?

DR. HANGER — I can cite an example in that connection. Just recently, one of our professors from France, very near the German border, was in this country and we were discussing the toxic effects of alcohol. He said that in his town, which is half French and half German, it was very noticeable how much more

cirrhosis there was among the French than among the Germans, who all take beer by preference. What there is in wine which makes it a biologic toxin is a question that interests us all. We all know the fat, well-fed Italian laborer who drinks wine with every meal, who is not intoxicated, and, yet, many of them do get fatty livers and cirrhosis.

Whiskey, to most people, is not a toxin. I think we can prove that. The problem is the man who is drinking, who does have an enlarged liver, and who does have increased fat. Some of these people are born with the defect. In my group of medical students there are always two or three on whom it would be interesting to have a medical biopsy. I think we could demonstrate increased fat in their livers even before they tasted their first liquor. Those people can be definitely damaged by alcoholic beverages. When they do not become complete teetotallers, I believe we can nurse them along.

PRESIDENT WILLIS — Thank you very much, Dr. Hanger. What you have said will be of great help to all of us in trying to classify risks properly, with the history of one of the commoner hepatic disorders. That is why we wanted to hear from you. We are very grateful for your fine contribution.

PRESIDENT WILLIS — The presence or absence of coronary artery disease causes medical directors more concern than any other question they have to decide. We all have cases with symptoms which may or may not be evidence of coronary heart disease. The next speaker's name and work are well known to all of us. He is Clinical Professor of Medicine at Harvard Medical School and physician to the Peter Bent Brigham Hospital of Boston. It is my pleasure to introduce one of the most eminent cardiologists that this country has produced — Dr. Sam Levine.

CORONARY ARTERY DISEASE

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The diagnosis of coronary sclerosis or coronary artery disease depends upon a few very definite findings. If a diagnosis of angina pectoris can be made, that patient has coronary sclerosis with few exceptions. This will depend largely upon the history, as is well known.

Another way of making the diagnosis of coronary sclerosis is by actually seeing the coronary artery sclerosed, on fluoroscopic examination. There are a certain number of cases in which coronary sclerosis can actually be seen and delineated. That is an anatomical diagnosis. That does not necessarily mean that the patient has angina, because angina is essentially a physiological diagnosis. It is inferred, when a patient has angina, that he is suffering from coronary disease. A few are not but most of them are. In the same way, a patient may have calcification of the pericardium. It is not necessarily constrictive pericarditis. Constrictive pericarditis is a physiological diagnosis, and calcification of the pericardium is an anatomical one. Likewise, we see occasionally calcified coronary arteries, and such patients generally have angina, but some do not. Their coronaries are calcified, but they are patent, and do not have the physiological manifestations that are called angina.

There is certain electrocardiographic evidence from which we infer that a patient has coronary artery disease, for example, classical evidence of myocardial infarction. However, there are a great many other abnormal electrocardiograms from which one infers that the patient has coronary sclerosis, but many mistakes are made.

It is not uncommon nowadays to have individuals classified as coronary cases, especially males and sometimes females over 50 or 60, when the electrocardiogram is found to be abnormal. They do not have hypertension, they do not have valvular disease,

and there is no good coronary history. Knowing that coronary artery disease is common at that age, they are classified as coronary cases, and the electrocardiograms are regarded as being compatible with coronary artery disease. That is a rather misleading and indefinite kind of report — "electrocardiogram is compatible with coronary disease". Any kind of an electrocardiogram is compatible with coronary artery disease. A normal electrocardiogram is compatible with coronary artery disease. We are therefore led to make that diagnosis on insufficient grounds.

In some cases the frequent use of cathartics with the accompanying diarrhea and the excessive loss of potassium will produce markedly abnormal electrocardiograms with inverted T waves. Such curves are likely to be diagnosed "indicative of myocardial damage", or "compatible with coronary disease". These persons will have normal hearts and the tracings will return to normal on discontinuing the cathartics.

Other cases, when properly investigated will be found to have very definitive disease of an entirely different nature. In this situation, there is a large group of conditions that have to be considered. Occasional ones have amyloid or sarcoid disease, a few have had pericardial constriction which will simulate coronary artery disease in a man over 60. They complained of atypical chest distress. What are men supposed to have after 60? They are supposed to have coronary artery disease. The truth is, they had abnormal electrocardiograms too, but a few little simple bedside points gave the clues. Their neck veins stuck out like fingers, even when they were sitting upright. They did not have paroxymal dyspnoea. The liver was enlarged. The venous pressure was 280, and we found pericardial constriction.

I mention this because we are too ready to throw all these elderly people into the waste basket of coronary disease, in the absence of good proof. If the patient has an attack of acute coronary occlusion with classic myocardial infarction, he is likely to have significant coronary artery disease. Bundle branch block, for example, is commonly associated with coronary artery disease, but there are a great many people who have bundle branch block, whose coronary arteries are free of any disease. We do not know

why some of them develop these abnormal tracings. Right bundle branch block is commonly found in people who live very long. It can be a residual condition following infection. It requires only a small inflammatory lesion in the musculature containing the left or right branch of the conduction system to produce abnormal curves. These patients recover and are well, possibly remaining symptomless for an indefinite length of time. To be sure, the majority of elderly people who have bundle branch block have serious heart disease. Many of them have coronary artery disease but the diagnosis is made by inference, unless we have the other evidence — the classical picture of myocardial infarction or classical angina pectoris, or visual coronary sclerosis, seen on fluoroscopy.

Let us go back to this old question of angina pectoris. If a patient has a classical story of angina, he has coronary sclerosis, or else he is a liar. If I went to a strange physician who did not know me and I described the typical story, he would just have to say I had angina pectoris. The history, when given in its classical fashion, is practically pathognomonic. Of course, the history can vary a great deal. It is not always clean-cut.

The Master's test is not pathognomonic of angina pectoris. A great many of our mitral cases, before operation, have a positive Master's test but they do not have coronary artery disease. If the patient has no other obvious heart disease and the differential diagnosis is no disease or angina, that presents the problem that particularly plagues those interested in insurance. Has the patient no disease of the heart, or has he this serious disease of the heart? Under those circumstances, a positive Master's test, I think, would sway us very strongly in the direction of coronary artery disease. It is a good deal more convenient than the oxygen test, which is used hardly at all in Boston.

There is another test which is highly regarded by some. It is the carotid sinus test. If a patient has a pain at the moment he is being examined, put a stethoscope over the precordium of the patient. If there is no nurse or resident physician present, have the patient hold the stethoscope there while listening. Then do not tell him what is being done, but massage the carotid sinus. When you do that for a few seconds and obtain slowing, good

slowing, from the carotid sinus reflex, release the pressure. Then ask the patient, "Is the distress that you had any worse?" Do not ask, "Is it better?" Ask, "Has this feeling become any worse than it was a moment ago, before I touched your neck?"

Try to mislead them. Do not ask a leading question, but try to misdirect them. Ask them, "Is that feeling worse?" If they say, "Why, no, doctor, it is gone," that patient has coronary artery pain. It is not biliary pain. It is not spondylitis. It is not functional.

If the heart has not slowed, there will not be any response and no inference can be drawn. In my own experience it has been practically invariably correct. There is something about slowing of the heart that relieves the pain. The pain has been observed to disappear while the heart was not beating. A very lengthy pause of the heart beat was obtained and, in that case, the patient was asked to use one word, "now", the moment the pain let up. While the heart was still in asystole, he said, "Now."

What can the mechanism of this phenomenon be? At first, because it acted so abruptly — not in minutes, but in seconds — it was thought to be a reflex. It is more logical, however, to believe that the heart slows enough and, during diastole (the coronaries are fed mostly during diastole and not during systole), the so-called "P", or painful principle in the heart, caused by lactic acid or other chemical, is washed out. More is washed out than is produced by the slow ventricular systoles that are taking place. The pain disappears. That test has been helpful at times, but of course no one needs it when the diagnosis is clear. However, when the diagnosis is somewhat puzzling and the physician can witness the attack that the patient evokes spontaneously, it may be very helpful in diagnosis.

In my practice two experiences are recalled with the same physician, a very able gastroenterologist in Boston who had a patient with gallstones. The stones could be seen easily in the x-ray. But the patient had some questionable symptoms in addition, and the consultation was desired because of those. My coming into the room brought on this little distress — a pain. It was not very severe but it responded within a few seconds to carotid sinus pressure. That was a new concept to this gastro-

enterologist, and he thought it was too foreign, so the patient left the hospital with a diagnosis of gallstones. The physician could not accept the additional diagnosis of angina. There was no question in my mind but that he had gallstones *and* coronary artery disease — a very common combination. A few months later the physician received word from the patient's wife that he had been found dead in bed. One does not suddenly die in bed from gallstones. He had coronary artery disease.

Some months later the same kind of a problem was encountered with the same doctor and, again, he was skeptical. This time, however, the patient left the hospital with the official diagnosis of gallstones and with a question of angina. Subsequent events also confirmed that diagnosis.

It has been found better to do this test with the patient lying down. It is a little safer to have the patient lying down when pressure is applied on the carotid sinus because he can faint. We do hear and read about instances of hemiplegia resulting from carotid sinus stimulation. A group of seven were reported out on the Pacific Coast and one of these seen by me was left with permanent paralysis which came directly after carotid sinus stimulation. This is not because the heart stopped. All the paralyses came on the side of the pressure. It was due to obstruction of the blood flow. The clinician kept his hand on the carotid artery for twenty or thirty seconds, possibly, and there was no blood going up to the brain. In older people with considerable sclerosis of the cerebral vessels, thrombosis can occur. If it were due to asystole of the heart, there would have been some with hemiplegia on the right and some on the left. The test has been done on hundreds, maybe thousands, of patients in my practice without an accident. Press for only a few seconds and release it to let some blood go through, and then try it again later on if desirable.

Usually when a diagnosis of angina pectoris is made we infer that the patient has coronary sclerosis. There are some exceptions, but not many. There are some younger people who have valvular disease and also have angina pectoris, but the coronary arteries are normal. The diagnosis is still correct, because, once the diagnosis of angina is made correctly, we say in effect, "That patient

is subject to sudden and unpredictable death." It may not come for twenty years, but he belongs to a group of people who have that hazard. It is an unpredictable hazard but it does exist.

In a large group of cases with angina it is known that about half of them will die suddenly. That also confirms the diagnosis because sudden death is not characteristic of conditions like glioma of the brain. There is something peculiar about the condition which involves that particular predicament and hazard. There are people with aortic stenosis and a few with mitral stenosis who also have angina pectoris, even younger ones whose coronary arteries are normal. There are very rare ones among patients with anemia. Most patients who have anemia and angina also have some coronary sclerosis. The anemia just uncovers the fact that they have coronary artery disease concurrently.

The same thing is true of thyrotoxicosis. There are patients who have thyrotoxicosis and angina. Cure them of thyrotoxicosis, and when they are a great deal better the angina may have apparently disappeared. But, they will have angina in walking hurriedly in cold air, whereas, before, they might have had the angina spontaneously, ten or twenty attacks a day. Only an extremely rare patient with angina and thyrotoxicosis will have normal coronary arteries at postmortem examination.

There are rare instances of angina occurring in amyloid disease. One such case had amyloid disease of the heart in which the heart muscle was riddled with amyloid disease. The coronary system was normal but the patient had angina pectoris. It is a very rare combination. Therefore, apart from these rare cases, when one says that a patient has angina pectoris and the diagnosis is correct, that patient also has coronary artery disease.

Before taking up coronary thrombosis, there are some things concerning the subject that should be discussed briefly. In the background of coronary artery disease, we are now greatly concerned with the question of diet. But what do we actually know about coronary artery disease? We know that there is a strong male predominance and there is no doubt about that. We know that there is a familial factor and there is also no doubt about that. When six people, all brothers and sisters, all have the same disease and die of it, statistics are unnecessary to tell us there is

something unusual about the original blastoderm from which those individuals came.

There is also a constitutional type and there is a good deal of overlapping here. The mesomorphic person is more likely to have it. The skinny individual, the man who has not been strong, is much less likely to have angina than the strong man who brags about his health. This is a common story that impressed me many years ago, and it was included in a paper written back in 1921. It is the fellow who says, "Why, doctor, I have not been sick for thirty years. I have not had a sick day. I can do the work of three men. But lately I have been having a funny feeling in my chest." That is the classical type of person who will develop angina. But the slim person, who has been sickly and feeble and neurotic or half well, has had a lot of other things the matter with him perhaps, but he does not get angina so readily.

We also know that the cholesterol in the blood is more often elevated in persons with coronary disease than in the controls. The same is true, for some unknown reason, concerning uric acid in the blood. Although the significance is not known to me, it is true that a hundred men who have angina or coronary artery disease at the age of 50 will more frequently have a high blood uric acid content without gout than would normal controls. This is before they have gout. Some develop gout later on and some never have gout. But the uric acid in the blood is abnormally elevated. This suggests some sort of a stigma.

There are some things we do not know about coronary artery disease. We talk about stress and strain but it is doubtful whether it means much, anyway. A great many people with coronary artery disease have not had any stress or strain at all. They do have a family history of coronary artery disease and they may never have had a worry in their lives.

Whatever constitutional factors there may be playing a role, they do not explain why young men in their forties, who have a coronary attack, will have the sclerosis in one coronary artery while all other arteries in the body will be normal. If a patient has a common duct stone and jaundice, the jaundice does not localize itself to one finger or one eye. If we have a general disease causing atherosclerosis it should produce changes in all arteries. Then why are

all the other arteries smooth and the left descending coronary artery blocked? This is not intended to suggest that there are no general constitutional factors involved. There must be some. But, it should be remembered that there can be something local in the heart to account for the localization of thromboses, narrowing or atheromatous arterial changes.

When we inherit a familial tendency to disease what do we actually inherit? We inherit anatomical structures, pigment in our eyes or in our skin, peculiar lobes of the ear or wrinkles in our brow. We inherit a physical trait. In the last analysis, somebody might find that the granules of a certain cell are different in one person than in another, and that is why one has hemophilia, or epilepsy, or some other hereditary disease.

Starting with the premise that there is something hereditary in coronary artery disease, what is it that we inherit? One thing which may be inherited is a peculiar anatomical architecture of the coronary arteries. This is a field of investigation that is terribly difficult. I do not know anybody who has gone at it vigorously. It would not require more than a slight difference in the turn or bend of a vessel, which, after forty years of torsion, would end up with a sclerosed plaque, a plaque which would not have been there had the vessel not been quite as angulated. That is something objective that a person can inherit. The minute differences among different people in the anatomical structure of the coronary arteries present a problem that deserves very careful study. It could easily explain many things seen but not understood. We know that trauma to vessels is injurious. We know that streams can produce fibrotic changes such as a fibrous plaque on the right ventricle opposite a ventricular septal defect where the left ventricle had pumped blood out through the opening producing a jet impact on the opposite heart chamber wall. Eventually, a little calcified plaque develops there. It requires no imagination to understand that. One might suspect that something of that order may be going on in the coronary arteries and that they are not all alike among different individuals even at birth.

There are at least two little clues that lend some validity to this hypothesis. Several years ago, Dr. William Dock published the results of studies conducted on the endothelial lining of the coro-

nary arteries in male and female infants. Even at birth, he found that males have areas of thickened endothelium, much more so than have female infants and also in those who die in the first months or first few years of life. There is then apparently a sex difference in the type of endothelial lining. This has been confirmed by others although there has been some dispute about it. It is a very important finding if it is true. It is the first hint that the male and the female coronary arteries might be different structurally, from the very beginning.

Some years ago Schlesinger in Boston found that there were three different kinds of coronary trees among humans. In doing his injection experiments, he found that in one group the left coronary artery covered some of the right ventricle in addition to the left ventricle. In another group, the right coronary artery did more than its share and supplied a fair area of the left ventricle. In the third group, the two were evenly balanced. There were, therefore, three different kinds of people: left predominants, right predominants, and balanced. The inference followed that if the left major coronary artery which happened to be supplying a good area of the right ventricle is blocked, a greater insult to the mechanics and the efficiency of the heart would result because a larger part of the heart becomes involved. That, also, is an anatomical difference which may explain certain things that can be seen clinically.

The point is, may there not be peculiarities and differences in the anatomical structure of the heart itself that can explain why some people are more vulnerable to coronary artery disease than others?

Another mysterious circumstance is that the patient with coronary artery disease has whatever structural abnormality that may exist all day long, but he has anginal pain for only five minutes. There must be some trigger phenomenon. The anatomical structure is not changing back and forth. He has aortic stenosis all day, but his anginal pain lasts for only five minute or three minute periods. What happens then? Where is the pain made? We are not sure. One may say that the pain is due to anoxemia. That is a rather odd statement — something is made by the absence of something else. It is more reasonable to believe that some-

thing is the result of the presence of something. The absence of oxygen may cause pain. The absence of oxygen can cause pain only if the absence of oxygen results in the presence of something else. Is it lactic acid? Is lactic acid the cause of the pain? Where does the pain arise? Does the pain arise in the muscle that is not being supplied well? Does the pain arise around the artery that is in spasm? Does the pain arise proximal to the artery from distention, like colic?

A good many of those questions are still unanswered. Anginal pain was reproduced in the dog by Doctors Sutton and Lueth many years ago by ligation of a coronary artery, allowing the dog to regain consciousness and then constricting the coronary artery by pulling on the ligature. The dog would go through some grimaces indicative of pain. That was very good evidence that local coronary anoxia causes pain.

Then, Dr. Louis Katz in Chicago did the same experiment but he put a cannula in the artery without obstructing the flow of blood at all. The pressure of the ligature caused the same grimaces. The inference there was that the pain was due to irritation of nerve plexuses in the vasa vasorum, and not to anoxia. We do not know, really, where this pain comes from.

There is something about an anginal episode that requires local trouble, while the heart is beating well, to produce pain. If the whole heart is feeble, patients do not have much pain. A patient may be dying — soldiers have been observed in the First World War bleeding to death, conscious until the last few minutes, and never having any pain. There must have been tremendous anoxia in the last half hour of life. But the whole heart was anoxemic. May it not be that one small part needs to be anoxic while the rest of the heart is beating vigorously to produce pain?

In some situations, pain disappears as the heart gets more feeble. Congestive failure at times causes remission of angina. In a patient with angina and thyrotoxicosis, under fluoroscopy the heart is seen to be beating vigorously and with great agility. After producing either a euthyroid or a hypothyroid state the heart beats feebly, with no angina. But, the output is now a great deal less than it was as, of course, and the demand is less with the lowered

metabolism. With the output less the pain disappears.

Anoxia was accepted too readily as the cause of pain in heart disease in general. It is suspected that when pain is present and if one could irrigate that coronary artery, not with oxygenated blood but with saline solution to get the irritating substance out of the localized area, the pain would go away. I am not so sure that the oxygen is as vital a factor in the production of pain as this metabolite.

There is also something about angina that resembles a conditioned reflex. People have attacks of angina frequently at the same time and as a response to the same kind of a cause. They may have it on the first hole of a game of golf and then it will be over. The man then plays seventeen holes without any trouble. He walks to the station in the morning, has his pain, gets it out of his system, and has no more pain the rest of the day. The same thing keeps recurring.

The actual foot-pounds of work that the heart does in a given time is generally looked upon as the determining factor in the production of pain (excess demand, insufficient supply, the equation of supply and demand). This all sounds logical, but there are some things that worry me about it. Individuals who work strenuously all day doing heavy work may never have a pain while they are at work. But, they can not walk one block to the streetcar when they get through work. The foot-pounds of work they did was much greater at one time, when they had no pain, than at another time when they had pain.

But what are these other factors? There certainly is a trigger mechanism, something that sets off the pain. Often the explanation of anginal pain at night in bed is that patients dream. If one can not get a story of a dream, it may be assumed that they had a dream that they forgot or had a subconscious dream. This is a rather loose, weak explanation. It is better to say that we do not know. These things are mentioned in order to leave the impression that there are many unanswered questions about this old story of angina pectoris.

A few remarks are necessary about coronary thrombosis. A bona fide diagnosis of coronary thrombosis, of course, means

coronary artery disease. Although this discussion was not meant to include anything about treatment, there is just one thing that should be recorded here because of my certainty about it. It is a little revolutionary and it is not easy for doctors to accept it, but the heart works less with the patient sitting in a chair than when he is in bed. If the therapeutic objective is to rest a heart, that patient will get more rest, have 20 to 25 per cent less heart work, if he sits in a chair with his feet down than if he lies in a flat position. Recumbency is a technic employed for generations because our teachers told us to do that. But the medical profession accepted something and they are going to have a hard time discarding it. The evidence is complete, both physiological and clinical. When a cardiac patient has dyspnea as a threat to life — and that is the main threat of heart disease — what does he do? He jumps out of bed. He wants to stand up. He knows better than to remain flat in bed and he has known better for centuries. If he is kept in bed it might kill him.

In an acute coronary attack, rest for the heart is imperative. If shock is present, one can not keep a person sitting up because he will simply faint. But, in the absence of shock, to decrease the work of the heart the patient should be out of bed and in a chair. When patients who had serious heart disease died in bed, the physicians were never blamed. Doctors are not criticized for those whom they have slain by keeping them in bed. The difficulty is that at the present time, and until we all grasp the truth of this, we will be thought negligent if something happens to patients out of bed. But, the patient's recovery will be enhanced if he has anything critically wrong with his heart, particularly with the left ventricle, if he sits in a chair with his feet down. The actual getting in and out of bed has produced no harmful effects and has not required lifting the patient. In fact, guiding and aiding the patient into a proper chair takes less out of him than actually lifting him. The procedure is just the same as getting him on to a commode. In my practice this method of treatment is used for acute myocardial infarction and many other types of heart disease and it convinces me that mortality and morbidity have decreased and the psychic state has been improved.

Dr. Donald E. Yochem — In the population as a whole, coro-

nary artery disease is considerably greater in the male than the female. However, in the female diabetic, the incidence of coronary artery disease is about equal to that of the male. Would you please comment on that difference?

DR. LEVINE — I am not sure that I am a good enough mathematician to decipher the figures there. I really can not answer it. I am aware that diabetes tends to equalize the incidence. Diabetes, I imagine, is more common in the female to begin with, is it not?

DR. YOCHEM — There is a very slight difference. It is a little more common in the female.

DR. LEVINE — I really do not know that I can answer that question. Coronary artery disease also levels out in the two sexes in the higher decades. From 70 years on there is not much difference between the female and male. To test a general principle — and this applies not only to coronary artery disease, but any disease in medicine — test it in the extreme instances. If one has coronary cases under 40, then what is the sex ratio? The difference is 25 to 1, not 3 to 1, as over the age of 40. Some twenty years ago we collected 100 cases of coronary disease under the age of 40 in Boston, and found that there were 96 males and 4 females. Then, as patients get older, the discrepancy becomes less and less.

DR. HARRY E. UNGERLEIDER — Dr. Levine, as you know, Blumgart and Schlessinger showed, in their pathological unfolding of the heart, that there are numerous cases in which these patients apparently were having silent occlusions and obstructions of the coronary system.

In life insurance medicine, those of us in its practice have to practice without history and without symptoms. Occasionally, the only thing we have is the electrocardiogram or the x-ray, as objective findings. We find these electrocardiograms showing us gross changes.

It has always been my impression that when one finds gross T-wave changes, from the life insurance standpoint, one must assume — or treat these patients as if they had, in fact, — a recognized myocardial infarction. I wonder if you would say a word about silent occlusion?

DR. LEVINE — I am glad you brought up that question. There are two or three times as many thromboses revealed by the Schlessinger technic than we ever get by a clinical story. What you say is true. Some episodes of angina not of long duration probably are thromboses. A man may never have been sick in bed at all and yet suffer an infarction. He may have classical angina off and on and yet thrombosis of a vessel may occur somewhere along the line. And there are some who never have pain and yet have a coronary thrombosis.

Clinically, I do not know how they can be diagnosed unless you obtain clues electrocardiographically. But the point that I wanted to make before was that not all these abnormalities mean infarction. Some of these abnormal T waves reflect myocardial disease of an entirely different nature. The insurance approach is still correct. Abnormal electrocardiograms are not desirable to have. The life span is going to be shorter. The insurance statistics were correct fifty years ago, when they said that a person with a murmur was an abnormal risk. That was at a time when my teachers said, "Oh, these functional murmurs mean nothing. A man will not get insurance, but he will live forever." Well, some of them did live but many of them did not. The insurance physician did not know what was going to happen to them.

It is true that "A hundred people with a systolic murmur will never live as long as a hundred people without a systolic murmur," because I have already lived long enough to see some of those with systolic murmurs that I called benign twenty or thirty years ago acquire calcified aortic stenosis. Years ago I overlooked congenital heart disease with a systolic murmur at the pulmonary area, to find out later on that they have atrial septal defect. The statistics were right. Good statistics, properly appraised, I think, will always be right.

The insurance companies have a great opportunity at the present time, with the mass of data that is being accumulated, to teach us a great deal. Large insurance companies must already have information to tell us whether people who work hard physically have less incidence of coronary artery disease than those who lead a lazy life. You probably have heard of the work that came out of England, showing that the bus drivers in London, who drive the bus,

have more coronary artery disease than the conductors, who are active. The mail carriers who tramp around all day have less coronary artery disease than the mail clerks who are indoors, doing very little physical activity. The figures they presented sound fairly convincing. However, I would welcome very much data of that sort from our own files. It is very important for us here to confirm the English figures. I believe that the insurance companies are in an excellent situation to answer some of these questions. The same thing is true of the mortality problem associated with smoking of cigarettes.

DR. JOHN R. MURPHY — Dr. Levine, in the early part of your talk and again later, you spoke of typical angina. There is some difference of opinion when people talk, as to what they mean by angina. I wonder if you would give us an example of what you mean by typical angina.

DR. LEVINE — I am glad you brought up that question, because it means a good deal to me. In the first place, I think that we should all try to put ourselves in a position to be able to tell a patient or his family that the patient has or has not angina. There is no room for terms like "mild angina," or "pseudoangina." Either you have diphtheria or you do not have diphtheria. Either you have angina or you do not have angina. At times I have to end up with a diagnosis of "Question of angina."

In making the diagnosis of angina, the classical story is nothing new. Heberden described it, but there are variations, I suppose, that Heberden himself did not see. He did not see all the different types. It is a distress, a pain, but more often a distress. Watch the patient describe it. "I've got this funny feeling here," and he brings his hands together over his chest. Or, "I've got this peculiar distress here," and he clenches his fingers. The neurotic will not do that, or a person with a benign pain. He is likely to say, "Oh, I've got this awful pain here" pointing to the apex or axilla. That is not a description of angina. The patient who has angina will say, "I've got this funny feeling here, as if something is expanding here. I want to get my shirt away." Or, the reverse, something is constricting. There are a variety of terms.

It is well to write down in your notes just what the patient says

and not put your words in his mouth. If you do that and review the data, there will be a certain number of people will give this reply, "I've got a peculiar feeling here and I don't know how to describe it." Put right down in your notes, "I don't know how to describe it." There are certain sensations that the patient is unable to describe because they are so odd. He will say, "I've got this funny feeling here, and I don't know how to describe it, and I don't like it. I don't know how to describe it." That is one expression.

Of course, it is more common centrally than at the apex. The radiation is also important. Sometimes it is only in the periphery, sometimes it starts in the periphery and goes centrally. More often, it starts centrally and goes peripherally, maybe into the jaw. There is no end to the type of descriptions. And yet, although they vary, there is still something uniform about them. In particular, by watching the patient's hands when he says, "I have this funny feeling here," you will see him clench or curl his fingers.

It is generally on effort, but it is not always on effort. I was mistaken on more than one occasion when I decided that it was not angina because the fellow could walk briskly. That is the most important, the most frequently precipitating cause — walking briskly. I do not know how walking does this but it is more difficult for a patient with coronary artery disease than climbing stairs. Indoors, that patient can do a lot, but he can not walk briskly out of doors, and especially uphill or in cold air. If the patient can walk briskly in cold air after a meal, upgrade, he does not have angina pectoris. He may have had a coronary attack and still be able to do that. The patient may have had a coronary occlusion and recover with a normal ballistocardiogram, but he does not have angina if he can walk upgrade. The ballistocardiogram may be normal after a coronary occlusion if the heart muscle is efficient. Ballistocardiography has come into play here, and we are going to learn a good deal more about its value, especially from an insurance point of view. I have an idea that it will tell us when a little "graying of the hair" is going on in the heart. When that will mature into disability is another story. It may be possible to guess by looking at a person, by his anthropological

physique and his family history, about as much concerning his future coronary course as would be learned from the ballistocardiogram. I mean that seriously. I could form an impression by looking at people as to whether they are good or poor candidates for coronary artery disease. It will not always be right, nor will one always be right about the ballistocardiogram. An abnormal ballistocardiogram may be just a little clue that this is the kind of person who is heading in the direction of coronary disease. But the speed at which he is heading that way is another matter. It is a wonderful thing that we do not know. It would be a tragic day, I think, when we doctors could tell the month, the day and the year when a patient will have a fatal coronary attack.

DR. W. H. HILL — I would like to ask Dr. Levine how to distinguish pain of an hiatus hernia from anginal pain.

DR. LEVINE — I do not believe that pain of hiatus hernia comes on hurrying or walking uphill or in cold air, (and not on walking gently) and is promptly relieved by stopping or by the use of a nitroglycerine pill. When a patient has pain corresponding to the above description and shows an hiatus hernia on x-ray examination, I believe he has two conditions, i.e. angina and hiatus, and many have both.

We shall not talk about a large diaphragmatic hernia but a small one. I think that the discovery of hiatus hernia in people has done more harm than good. I do not believe that people with hiatus hernia have distress of the anginal type, that is, distress which is precipitated by their walking briskly in cold air, and being relieved when they stop or with nitroglycerine and in addition having the customary radiation characteristics. When they have this typical story and also have an hiatus hernia, they have two diseases. I have seen hundreds of people, literally, who have hiatus hernia and angina, and the angina might have been ascribed to the hernia, but they have followed the path of coronary artery disease.

Now, there is diaphragmatic hernia, with irritation, cramps, pain, and bleeding, that can simulate an acute myocardial infarction. When you see something resembling coronary artery disease in an obese woman, never known to have had hypertension or

diabetes, then we say, "Let's wait until that first stool comes through and see if it is not black or bloody." Look for diaphragmatic hernia. But, do not accept hiatus hernia too readily as an explanation of pain that you otherwise would call anginal pain.

DR. GEORGE MCLEAN — I would like to ask Dr. Levine if he would care to comment on some of these diagnostic and prognostic biochemical tests in coronary disease.

DR. LEVINE — The new enzyme methods?

DR. MCLEAN — Yes.

DR. LEVINE — I would rather not for I know too little about it. That is new investigation about which we will hear more in the coming year.

PRESIDENT WILLIS — Dr. Levine, we are extremely grateful that you were willing to give the time to come from Boston to address this group. What you have said will be most helpful to all the members of this Association. Thank you again.

Anything new in the treatment of cancer is of interest to every member of this Association. The reason is obvious. We are particularly fortunate in having, as our guest speaker, Dr. Joseph H. Burchenal, Professor of Medicine, Cornell University Medical College, Chief of Clinical Chemotherapy at the Sloan-Kettering Institute, Attending Physician and Chief of Chemotherapy Service at Memorial Hospital, New York City. His subject is, "Chemical Treatment of Cancer."

CHEMICAL TREATMENT OF CANCER

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The incidence of carcinoma is much greater than other forms of cancer, particularly the group known as lymphomas. Carcinoma, therefore, is of special importance in life insurance medicine and a major part of this discussion on chemotherapy will concern that type of malignant disease. It is well known that current effective methods of treatment are limited largely to surgery when the tumor is localized and can be resected, or to radiotherapy of the massive obliterative type. When the tumor is widespread, radiotherapy is only a palliative measure. The third field of treatment is the one that has the greatest promise for the future, but perhaps the least to offer at this time, that is chemotherapy or chemical treatment.

It is obvious that the chemical treatment of cancer should never be used when surgery or radiation might effect a cure. Likewise, if the disease is semi-localized so that it can be radiated with fairly large doses in several different places in the body, that is the therapeutic agent of choice. A chemical agent is useful when the disease is widespread and beyond the scope of x-ray and surgery.

Today is the age of chemotherapy. The last twenty years have witnessed the cure or complete subjection of most of the diseases caused by bacteria, rickettsia and protozoa. Although considerable progress has been made in the treatment of cancer, including the lymphomas and leukemias, it has not been nearly so pronounced as in the infectious diseases. There is promise that this can be changed in time but there are a good many difficulties to be overcome. This discussion will cover some of these briefly.

The differences and the difficulties encountered between the chemotherapy of infectious disease and that of cancer are fairly obvious. For instance, to destroy the streptococcus by sulfanila-

mide, one has to deal with a single-celled organism which is a relatively uncomplicated invader with certain nutritional habits. One of its requirements for nutrition is paraamino benzoic acid, a compound which cannot be utilized by the more complex host, man. Man requires a substance considerably more complex than this, actually, folic acid. He cannot synthesize folic acid from paraamino benzoic acid, whereas the bacteria can do this.

Therefore, since man does not require paraamino benzoic acid and the bacteria do, the introduction of an antimetabolite might destroy the bacteria without harming the patient. Sulfanilamide is such an antimetabolite and is closely enough related to paraamino benzoic acid to enter the same enzyme system. Once it gets in there it is just sufficiently different to effect obstruction to the function of the enzyme system making it impossible for the organism to utilize more paraamino benzoic acid.

This is analogous to a lock with two keys both on the same blank. One of them, the metabolite, has notches in the right place. Not only can it be put in the lock but it can be turned once it gets in. The antimetabolite is made on the same blank and will go into the lock, but the notches are in the wrong place. Once it gets in, it cannot be turned and the lock is thereby obstructed so the right key cannot be put in. Therefore, by giving sulfanilamide, paraamino benzoic acid is antagonized in a system of two different organisms, one of which requires it, the streptococcus, which is severely damaged, and the second, man, who does not require it and is not harmed at all. This is an example of selective action.

In addition, if 99 of every 100 bacteria are eliminated, the body has defenses against the last few. That is not the case with cancer. In the first place, the cancer cell arises from a normal cell. It is a normal cell which, by mutation, has escaped control but it is not far removed from the normal. In some types of cancer, this relationship is closer than in others.

The process of finding a compound which will selectively damage the cancer cell or kill it without killing the normal cell is a very difficult undertaking. There are compounds which will damage the cancer cell to a substantial degree without damaging the normal cell. However, there are not any available which will

obliterate the cancer cell completely and not vitally damage certain essential cells.

In the second place, if the agent is able to eliminate most of the cancer cells, the body still cannot resist or destroy the remaining ones. As far as is known, the body itself has no resistance, or at least it has not been proven, because these cells arise in the same body and, antigenically, they have not been known to be different as yet.

Certain advances in chemotherapy or in cancer research during the last few years should be mentioned. The first one or two are largely theoretical. One of these is the removal of mysticism from cancer. It has been said by many able men that cancer is a very mysterious thing, and until the secrets of life itself are known, one could not expect to know how the cancer cell was different, and, until this was known, nothing could be done about it. Such reasoning is not necessarily completely correct. Suppose the cancer cell is considered as the causative organism of the symptom complex known as cancer. In that case, the postulates of Koch in which the organism causes the disease, are quite well filled by the cancer cell. According to these principles, the organism must be present in the affected tissue. In infected tissue, one finds the germ but in cancer tissue, one finds the cancer cell. The organism must be cultivated outside the body. That has been done in the case of cancer. Human cancer can be cultivated outside the body, both in experimental animals and in the test tube. The HeLa cell came from a carcinoma of the cervix and has been used extensively in tissue culture work and in many virus studies. It is used almost as a standard cell medium.

Tissue cultures of carcinoma of the cervix, very widely metastatic, have been grown for many generations in a test tube, then replanted into the same patient, causing a localized growth which was surgically excised and proven to be histologically the same as the original tumor. Although not one of Koch's postulates, it is well known that almost all organisms that respond to chemotherapeutic agents, develop resistance to them after persistent trial. Certainly, this is also true of the cancer cell. If anything, the cancer cell has a better facility for developing resistance to chemical agents than have bacteria.

The second theoretical advance of particular interest is the fact that five or ten years ago, it was not easy to arouse the interest of the biochemist in any of the problems dealing with cancer. That is no longer true and some of the best biochemists in the country are engaged in work on these problems which is an extremely important feature. This is the source of new compounds, new ideas, and the new substances produced in chemistry laboratories give promise of eventual effectiveness. The interest of clinicians now extends into this field. In previous years, the patient was referred to the radiologist and then to a nursing home as nothing further could be done. Now, however, internists are becoming more interested in what they can do to make the patient more comfortable and to keep him alive longer.

One of the more objective advances has been the growing of human tumors in tissue culture. This has been done not only with the HeLa cell itself but with many cells in tissue culture which originated in humans. Dr. Osgood reported recently on his success in growing a human leukemic cell in tissue culture in quantity. There may still be a question of whether these are necessarily leukemic cells or other cells of the bone marrow, but they appear to be leukemic cells. It is presumed that the proof of their leukemic nature awaits the demonstration that they can proliferate in the marrow and peripheral blood of the cortisonized or irradiated experimental animal.

The ability of cells to grow in the heterologous host will have great promise in the future. For example, Dr. Toolan, of the Sloan Kettering Institute is growing tumors of this type, one of which is a sarcoma taken from the calf area of the leg of a man. Similar work is being done elsewhere. Tumors of this kind in the hamster have grown from two millimeters to several centimeters diameter in a period of eighteen days. It is now possible to harvest literally pounds of human tumor tissue each week from one of these and to do metabolic and incorporation studies on it. These studies are extremely important. A satisfactory arrangement has now been made to test new chemical agents against these tumors. That constitutes another real step forward. The animals must be cortisonized before the tumor will grow, which means that cortisone is administered immediately before the tumor is transplanted.

These human tumors will also grow on the chorioallantoic membrane of the developing chick embryo. This is a very useful system because the tumors grow there without any cortisone and there are no complicating factors. Of course, one must realize that the chick embryo is quite different from a chicken. The work of Dagg and Karnofsky showed that if these chicks with tumors are allowed to hatch, the tumor metastasizes. Soon after hatching, the chick will be riddled with tumor metastases. They have no resistance against it because the tumor was implanted in the embryo. They require no cortisone or x-ray irradiation or any other measures to keep the tumor growing. Eventually they are killed by it. Death occurs in five to ten days with visceral metastases and in eighteen to twenty days when the metastases are in superficial tissue.

These tumors, of course, afford a good chance to test compounds. If this continues to a stage where all human tumors can be grown with a high degree of regularity, every patient with a tumor could have a biopsy when first seen. Then the tumor could be grown in many animals permitting a large number of agents to be tested against it and one could have a good idea of just which one to use clinically without having to try all agents on the patient to find out.

How does one go about finding these agents for clinical trial? There is a tremendous amount of interest and clinical panels have been established under the auspices of the National Institute of Health and the American Cancer Society as well as the Damon Runyon Fund to study this. There are two general methods whereby compounds are found. One is a fundamental approach to find a chemical difference between a cancer cell and a normal cell. On that basis it is determined what compounds should be used to kill the cancer cell. This would be an excellent method if there were real qualitative differences between the two cells, which is not the case. There are certain quantitative ones, but they are relatively unimportant. So far, it has not been possible to predict in advance the need of any particular chemical agent.

On the other hand, as is well known, that was not done in chemotherapy for infectious diseases. Many or most of the antibiotics including sulfonamide and penicillin were found by chance

rather than by careful synthetic methods. Even quinine was discovered in that way. The second way, therefore, is to study these compounds empirically, using some type of screening system by which a few are selected with at least a higher chance of favorable activity in man.

There are many such screening programs in process in different parts of the world. The one at the Sloan Kettering Institute has tested about 15,000 compounds of which the chemical structure is known. In addition to these, there are almost an equal number of antibiotic filtrates, all of which have been tested against mouse tumors.

Admittedly, it is perfectly possible that some compound which might be effective against human tumors, would not have any effect against mouse sarcoma 180 and, therefore, would be lost. While this is true, it is a chance that must be taken. Obviously, one cannot try 20,000 new agents against patients. It is, therefore, necessary to have some way of screening the agents. If the compounds prevent the growth of the single mouse tumor, it is tried against mouse leukemia. Then it is tried against many different mice with many different tumors, for its effect on the developing chick embryo, and also against normal and neoplastic cells, grown side by side in the test tube by tissue culture technics.

If it is effective by several of these technics, as a good compound usually is, there may be a decision to try it clinically. First, it must go to the pharmacologist, who tries it out on dogs, cats, and rats. The clinician first wants to know the maximum dose tolerated by a dog over a two week period given in daily injections. It is known that children and also adults usually will tolerate about the same dose as the dog on a milligram-per-kilogram basis.

The second thing the clinician wants to know is what organ system fails first in a dog that receives a minimal lethal dose. Is it a hepatotoxic agent? Does it destroy the bone marrow? Is the damage in the kidney or intestine? Once those data are available, the clinician is prepared to try it on a patient with very far advanced carcinoma. A very small dose is used at the beginning, gradually being increased to what is estimated to be the thera-

peutic dosage. Sometimes, it is necessary to go considerably higher because occasionally, man will tolerate considerably more than the dog. Once the patient receives the maximum tolerated dosage, the effect on the tumor is observed. If there is no benefit, then the compound must be tried on many other tumors.

Finally, if the compound has a favorable effect on tumors or leukemias, it is necessary to have a practical assessment in relation to other methods of therapy on a large number of patients. If a good compound becomes available, arrangements have been made through various organizing groups in Washington to test it rapidly in many different cooperating hospitals. In this way, the compound can be thoroughly tested and compared with existing means of therapy.

In the present status of chemotherapy there are agents of definite usefulness in acute leukemia, such as amethopterin, cortisone and 6-mercaptopurine. These are really members of three different groups of agents — the folic acid antagonists, the steroids, and the purine antagonists.

In chronic leukemia, there are the mustards, 6-mercaptopurine, cortisone, and urethane. In lymphomas, and polycythemia the mustards are the most useful. In multiple myeloma, urethane and cortisone are used to some extent. In carcinoma of the breast with cells still fairly closely allied to the normal cells, indicating some hormonal dependence, the androgens and estrogens are effective.

In the premenopausal woman, whose tumor presumably is being stimulated by ovarian secretion, one can treat it with androgens and obtain a fair degree of improvement. It is much better, however, to remove the source of the estrogens by oophorectomy. In the postmenopausal woman, estrogens can be used as the tumor is presumably growing in a medium with little or no estrogens.

Cortisone has only slight effect in the premenopausal or postmenopausal patients. Nitrogen mustard and triethylene melamines as well as some other compounds, have some effect.

In carcinoma of the lung, nitrogen mustard seems to be particularly effective as far as carcinoma itself is concerned. The term, particularly effective, is used in a strictly relative sense. There is more reason for using nitrogen mustard in carcinoma

of the lung than in carcinoma of any other tissue at this time. Triethylene melamine is also fairly effective.

In carcinoma of the prostate, estrogens are an excellent form of therapy. Some of the best results have been obtained in this field with some of the longest survival periods. The combination of castration and administration of estrogens is also effective.

In carcinoma of the ovary, with widespread metastases, triethylene melamine is effective as a palliative agent.

Nitrogen mustard is the basic drug of the mustard series. This series is known by the term of "polyfunctional alkylating agents". The idea being that they have two reactive groups which, presumably, act as alkylating agents. This characteristic is common to all the agents in the group. The chief difficulty with the original mustard was in its having to be given intravenously. It also caused considerable nausea and vomiting.

Investigators would like to improve nitrogen mustard so that it would have a better effect on cancer and also to make it easier to give, perhaps by mouth. It would be desirable to change the product in a way to eliminate the reactions of nausea and vomiting. One way of changing the situation is to add something in place of the methyl group. A compound being studied clinically now, is known as CB-1348. This compound is synthesized at the Chester Beatty Institute in London and it has a phenylbutyric acid group instead of the methyl group. It can be given by mouth and does not cause nausea or vomiting and it seems to be quite effective in Hodgkins' disease and some of the lymphosarcomas as well as in chronic lymphatic leukemia. The compound is still being used in the experimental stage, however. The alkaline fluids of the body cause this compound to form an ethylene imine ring and for that reason, various compounds with this same type of ring have been studied. Triethylene melamine with a similar ring behaves like a nitrogen mustard. It has the advantage that it can be given by mouth and causes relatively little nausea or vomiting. On the other hand, it is not absorbed with uniformity and the dosage varies from patient to patient and from time to time.

Another compound with the center ring replaced by a phosphoric

acid is known as triethylene phosphoramide. It is useful, but not much better than triethylene melamine.

Still another closely related compound tried recently, is known as triethylene thiophosphoramide. In this one, the sulfur radical is replaced by oxygen.

There is no satisfactory proof of any really great difference among these compounds. However, a large scale study on a nationwide basis is planned, involving their use in a large number of cases of carcinoma of the breast and various other types of carcinoma using triethylene thiophosphoramide in comparison with the ordinary nitrogen mustard. Past experience indicates that almost any cancer will occasionally yield to nitrogen mustard but the compound does not do this with any very high degree of regularity.

Another compound, known as Myleran has two reactive groups, one at either end of the formula, so that it fits into the group previously discussed. It was developed in England and is very useful in treatment of chronic granulocytic leukemia. Presently, it is the best chemical agent for that particular disease. It can be given by mouth, is absorbed well, and can be continued over long periods of time without nausea or undesirable side effects, other than depression of the bone marrow platelet formation if excessive doses are given.

In acute leukemia, therapy with any of at least three different classes of agents can result in a return of the bone marrow to normal status with normal erythrocytes, myeloid element, myelocytes, metamyelocytes, polymorphonuclear cells, and a return of the megakaryocytes. All formed elements of the blood can return to normal levels.

What agents are available for use in acute leukemia? There are the steroids and also two different kinds of antimetabolites. The formulae for these are extremely complex, including that for folic acid. This is a harmless vitamin essential for the growth and maturation of normal erythrocytes and normal leukocytes. Also, unfortunately, it is extremely necessary for the growth of certain types of leukemic cells, particularly in the acute leukemia of children. By making a single, slight change in the molecule

of replacing the hydroxyl group in the 4 position to an amino group, the compound becomes a very toxic agent, known as amethopterin. The trade name for this is Methotrexate. An increased sensitivity to both of these allows selective poisoning of the leukemic cell with doses which are not harmful to the patient and, in fact, will not inconvenience the patient at all.

It is true that there are borderline cases and many patients eventually require high doses. With larger doses, these compounds are toxic to the patient as well as to his disease, but there is sufficient selectivity in some patients to give excellent results with those agents.

They are particularly useful in the acute leukemias in children. In our experience, however, they have not been of much value over the age of ten years. There is recent evidence suggesting that perhaps treatment with a purine antagonist first and then later with Methotrexate may lead even adults to respond to the antifolic compounds.

The purine antagonist is another type of antimetabolite. Adenine is 6-amino purine which is common to all cells. It is present in the nucleic acids of cells and has an amino group in the 6 position. Mercaptopurine is a compound with an SH group in the same position. That is the only change from the basic structure of the molecule and it is a powerful antimetabolite. Another related compound, 6-mercapto-2-amino purine has no particular advantages over mercaptopurine. Still another compound, 6-chloropurine apparently acts in much the same way as 6-mercaptopurine. There is a very slight suggestion which has not been proven that this compound may be more effective in adults over 40 who have acute leukemia. Over the age of 40, remissions with the purine antagonists are fairly rare but they may be a little more frequent with 6-chloropurine than with mercaptopurine. Young adults about the age of 20 years ordinarily respond fairly well to these drugs.

The following case record illustrates what can be accomplished in acute leukemia with 6-mercaptopurine, thioguanine or 6-chloropurine. A girl had a leukocyte count of 160,000, a marrow filled with blast cells, 19,000 platelets and 9 per cent polymorphonuclear cells. On therapy with mercaptopurine there was a rapid

fall in the leukocyte count. A gradual increase occurred in polymorphonuclear cells to above the 50 per cent level, platelet count returned to normal at the 300,000 level and the marrow changes gradually returned to normal.

Another patient with chronic granulocytic leukemia was treated with mercaptopurine resulting in a dramatic reduction in the size of the spleen. There was undoubtedly a tremendous outpouring of debris from the great loss of tissue represented by the decrease in the size of the spleen. Her leukocyte count before therapy was between 400,000 and 600,000. It decreased rapidly under therapy. When treatment was discontinued for a period of about a month, the leukocyte count immediately increased again. When therapy was resumed, the disease went into excellent remission and her condition has been satisfactory for over two years.

The Parke, Davis Company sponsored research on a filtrate and finally produced a crystalline compound with the structure diazoacetylserine (Azasevine). This was very effective against a large variety of animal tumors. Unfortunately, when used alone, it is of no practical value on human tumors. It causes slight remissions in acute leukemia and some slight remissions in Hodgkins' disease. While not a practical agent, it is still a very interesting one.

The synthesis of these compounds is a very complicated process. It is obvious that they begin with very simple building blocks progressing in the direction of nucleic acids. As the building blocks are added there are certain levels where folic acid antagonists or the purine antagonists or azaserine act to block the formation. For example, the synthetic pathway may be blocked by the antifolics at one place, azaserine at another and again by antifolics and finally by mercaptopurine. The important thing to realize is that with none of these combinations has it been possible to get 100 per cent blockage in the leukemic cell. To do this would also result in the death of the patient. The best that can be done is to give enough of the drug to attack the leukemic cell with moderate intensity at a level which still will not injure the patient. Perhaps if this is done two or three times along the same level, some synergism or cumulative effect might be possible. That is what some believe has been accomplished to a certain extent.

Azaserine alone is fairly useless. Mercaptopurine is useful for a temporary period of time in acute leukemia. By giving these two drugs together, it appears that the combination is successful in delaying the development of resistance to mercaptopurine by two or three months, and in some cases, much longer than that. The effect of mercaptopurine on some tumors was also enhanced by the combination.

One child, three years old, with acute leukemia was treated with the combination for about 18 months and she is still in remission on these drugs. Using mercaptopurine alone, the longest remission previously observed was for a period of about six to eight months. This, however, is the best result in our experience.

A series of 218 cases of acute leukemia in children was collected from the literature by Tivey. They were treated with blood transfusions, a certain amount of antibiotic therapy but with no specific form of anti leukemic therapy. Five per cent of these survived one year from the start of the disease and 50 per cent of them died under four months from the beginning of their condition. These results are compared with a group of 154 cases treated at Memorial Hospital with cortisone and amethopterin using either one or the other and sometimes both. Twenty-nine per cent of this group survived one year from the start of their disease. In another group of 143 consecutive cases with acute leukemia in children, 47 per cent survived twelve months from the beginning of the disease.

It may be said that there is little difference in the survival rate among these children but at least they are healthy most of the time, going to school and living fairly normal lives until a month or so before the terminal phase of their disease.

This review does not reveal much of value in the chemical treatment of cancer at the moment. However, in children with acute leukemia, it is our opinion that something has been accomplished. If a successful method of chemotherapy is developed for acute or chronic leukemia, then effective treatment for other forms of cancer should follow soon. It is unlikely that the cure for cancer will be a cure for every type of cancer. It is probable, for example, that cancer of the prostate will yield to one type of drug, cancer of the lung may require another and perhaps, even

in epidermoid cancer of the lung, there may be differences in the biochemical characteristics which would require several different agents to control all the different types. It is my opinion that those can be found.

DR. CABOT LULL — Dr. Ewing used to tell me, long before any therapy was started, that the first types of tumors to be attacked probably would be Hodgkins' disease and leukemia, and it seems to have turned out that way. Is there any particular reason why these are responding more than the carcinomas?

DR. BURCHENAL — It is hard to say why they are necessarily responding. I can tell you one reason why we use them. We are very anxious to see the effects of the agent which we are using on the tumor cell. If you have a patient with carcinoma of the stomach and you give him an agent, and the next day you want to see what is happening to the tumor, and keep on doing that daily, a zipper opening would be needed on the abdominal wall, which the surgeons have not yet been able to give us. On the other hand, with leukemia, we can puncture his finger and look at the cancer cells ten times a day, or take the marrow and see where they are being formed. That is one reason.

I do not know why the chronic myelocytic leukemias, for instance, respond so well. They respond to a multiplicity of agents. Lissauer, back in 1865, found that arsenic was extremely helpful in those diseases. They respond to x-ray and many other things. Acute leukemias of children respond better than the acute leukemias of adults. As far as tumors go in the two age groups, acute leukemia is relatively much more common in children — it represents 50 per cent of all cancers in children, whereas, in adults it is a much smaller percentage — children for some reason or other, seem to respond. I do not know why it is so. Perhaps their tissues are growing differently. Perhaps it is a question of hormones.

DR. B. T. D. SCHWARZ — What is the effect of Krebiozen? Do you have any experience with that controversial product?

DR. BURCHENAL — We have had no experience with it at all, but, to the best of my knowledge, through talking with a great many people who are working in the field and who have been

in Chicago and have seen the data, I do not know of any evidence that it is effective.

As you may know, it is easy to claim that a compound has an effect. It is very easy to get a subjective effect particularly in patients with cancer. In a patient who is deathly ill, particularly if he knows what he has, an enthusiastic doctor who injects him with distilled water, is likely to get an effect. In other words, the patient wants very much to get well. As far as I know, with regard to Krebiozen, I have not personally seen any evidence that it does anything.

DR. RICHARD S. GUBNER — Is there any recent development with Coley's toxin? I know that the younger Dr. Coley had been working as recently as a few years ago with it and wonder what the present status is.

DR. BURCHENAL — It is still being used to a certain extent in Ewing's tumor, where the patient first gets large doses of radiation of the tumor to obliterate it and then Coley's toxin in the hope that there may be some additive effect. I do not think that Dr. Coley feels that it has any real practical use anywhere else. I am speaking of Dr. Bradley Coley now. I am sure that he does not feel very strongly about its usefulness. One is confronted with such a hopeless situation in Ewing's tumor, anyway, it is hoped that something else might have an effect.

The work with Shear's polysaccharide which is a purified product derived from Coley's toxin is about to be reported, by the group at the Institute for Cancer Research in Philadelphia, at the Lankenau Hospital. That group did find a fairly high percentage of temporary regressions in patients with lymphoma, primarily, but also some other carcinomas. But, it must be emphasized that they were very temporary regressions.

PRESIDENT WILLIS — Dr. Burchenal, your intimate knowledge of the new developments in the treatment of cancer leads us to hope that vastly important discoveries may come from your work and the work of your associates at the Memorial Hospital. We are extremely grateful to you for talking to us today. Thank you, sir.

Peptic ulcer may occur more frequently in medical histories of applicants for insurance than any other important disease. The next speaker is a highly qualified authority on gastroenterology. The title of his paper is, "Prognosis in Peptic Ulcer Disease." Dr. Henry L. Bockus is Professor and Chairman of the Department of Medicine, Graduate School of Medicine, University of Pennsylvania, and Chief of Staff and Chairman of the Department of Medicine of the Graduate Hospital, Philadelphia. It is a great pleasure to have Dr. Bockus with us.

PROGNOSIS IN PEPTIC ULCER DISEASE

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To be a statistician on this occasion would be preferable because there is so much factual data needed in order to intelligently discuss the prognosis in peptic ulcer disease. Much research needs to be done in this field. "Peptic ulcer" refers to what is generally known as chronic peptic ulcer, the lesion that has penetrated the mucosa and the muscularis mucosae to the submucosa. The term does not refer to erosions or acute ulcers.

This disease is the most common organic cause for recurring dyspepsia in the male. The incidence is not precisely known in any one country. The figures of somewhere between five and 12 per cent for the United States, are based for the most part upon autopsy reports of open ulcers or scars. A more recent clinical survey, by Dahl and Jones (1951) in London, on live material, outside the hospital, suggests an incidence of peptic ulcer (active ulcer or history of ulcer) of about 5.8 per cent among males between the ages of 14 and 64 years, and of 1.9 per cent among females.

There is little doubt but that peptic ulcer disease is on the increase. Vital statistics in this country showed a mortality of 2.7 per 100,000 in 1900 as compared with 9.4 per 100,000 in 1953 — about a three-fold increase. In this country, peptic ulcer ranks about tenth as a cause of death, and about twelfth in days lost from work (Ivy, Grossman and Bachrach), so it is a rather common and important disease. Ivy has estimated, by a review of statistical material, that about 360,000 patient-visits to physi-

cians for peptic ulcer disease occur each month in the United States.

There is much to be learned concerning geographic and racial influences in the occurrence and behavior of peptic ulcer. Among the Bantu tribe in southern Africa the incidence of ulcer is only about one-tenth that among white men in the same area. But, when the Negro comes to Chicago, the incidence of ulcer is about the same as in the Caucasian. That may have some significance. The Chinese, living in Java, develop ulcers ten times more frequently than do the native Javanese. The north Indian rarely acquires an ulcer, whereas the south Indian does. One may continue to cite differences of this type, yet the reasons for such variations are not clearly understood. There are many influences at work, and the statistics in some instances are probably not totally reliable.

Very recently, de la Vega analyzed the records of 300 patients with active peptic ulcer, proved by x-ray. The material was obtained from the out-patient department of the Hospital de Enfermedades de la Nutrition. The purpose of the study was to determine whether the behavior of the disease differed in any way from peptic ulcer occurring in the United States. It is rather interesting to note that half of his patients were Indians or mestizos and the other half were Caucasians. There was no difference in the incidence or the behavior of the ulcer disease in these two races in Mexico, but he found a striking difference in the behavior of peptic ulcer disease in Mexico as compared with that in the United States. The ratio of gastric ulcer to duodenal ulcer in Mexico is the same as it is here. However, the complications of hemorrhage, perforation, and obstruction occur in only half the number of patients there as compared to the rate of occurrence in this country. Furthermore, the degree of acidity in the stomachs of Mexicans with ulcer is in the neighborhood of one-half that recorded for patients in the United States. The reason for these differences is not known. Studies as accurate as this one carried out in various parts of the world could contribute important information.

The social stratum of the patient with ulcer was believed to be significant because of that old and often quoted paper from London

indicating a much higher incidence of gastric ulcer in people from the lower stratum of London society as compared with those in the upper walks of life (Jones). A good deal has been written concerning the influence of various occupations upon the occurrence of ulcer. The physician, the business executive, the bus driver, the energetic person — all these were thought to be more susceptible to ulcer. The agricultural worker was considered to be more immune. More recent statistical reviews do not so definitely suggest a close relationship between occupation and the occurrence of ulcer. If there is one profession that shows a true statistical increase in ulcer disease, it is that of physicians. This may be because the doctor is investigated more thoroughly, perhaps, than some other people. Other observations, such as the fact that fishermen in the north of Norway have gastric ulcer two or three times as often as the Norwegians thereabouts in other occupations, are difficult to explain.

PROGNOSIS

The following discussion concerns some of the factors which are thought to influence the prognosis in peptic ulcer disease, both from the standpoint of morbidity and mortality.

Site of the Ulcer. There are a number of people who believe that duodenal ulcer is actually a twentieth-century disease. Perhaps it is, because before the twentieth century not very much was known about it. It was reported in 1827 but, actually it attracted very little attention until almost a century later. In the United States clinicians report that at the present time duodenal ulcer is from three to ten times as common as gastric ulcer. These figures are derived from the clinicians' experience with the disease. However, based on autopsy evidence, gastric and duodenal ulcers occur with equal frequency. What is the reason for this? It is presumed a good many duodenal ulcers' scars escape detection at autopsy. In other instances the ulcer may have been too small to give rise to recognizable cicatrix. Furthermore, there are more gastric ulcers found in each age group when autopsies are performed in hospitals.

As to the site of ulcer in relation to the prognosis, there is general agreement that gastric ulcer is the greater killer of the

two. The statistics in 1947, from the Registrar General's office in England and Wales, showed that there were 3000 deaths from gastric ulcer that year as compared with 1800 from duodenal ulcer. The incidence of hemorrhage is greater in gastric ulcer, and the mortality from both massive hemorrhage and perforation is greater in gastric ulcer. The higher mortality in gastric ulcer may be due in part to the fact that the average age of patients with gastric ulcer is about ten years older than those with duodenal ulcer.

Another factor of great importance is that gastric ulcer shows a much greater tendency to be associated with other serious organic disease than does duodenal ulcer. In reviewing the deaths from complications of peptic ulcer disease, one is impressed by the influence on mortality which is exerted by arteriosclerosis, cirrhosis of the liver, prostatic, pancreatic, cardiovascular, and biliary tract disease. These conditions, when present in the patient who develops a complication of peptic ulcer, definitely increase the mortality from that complication. Another thing which influences the prognosis in gastric ulcer is the fact that an *erroneous diagnosis* is established more often by the clinician in gastric ulcer than in duodenal ulcer.

The postbulbar location of duodenal ulcer definitely influences prognosis unfavorably. In postbulbar ulcer the diagnosis is established with greater difficulty. It is often missed. The success with medical treatment is not as great as with bulboduodenal ulcer. The complication of hemorrhage is at least twice as great when the ulcer is in the postbulbar area as compared with ulcer in the cap. Postbulbar ulcer presents a more difficult problem to the surgeon because an operation here is much more difficult than one for bulbar ulcer near the base of the cap, for anatomical reasons.

Age. Age exerts an important influence on the prognosis in ulcer disease. Formerly, peptic ulcer was thought to be principally a disease of youth but there are now more and more instances of it later in life, so that the average age incidence of peptic ulcer disease is gradually increasing. Actually, vital statistics in the United States show the age peak for mortality from peptic ulcer to be between 65 and 69 years at the present time. Sixty-two per cent of the ulcer deaths in Norway, several years ago, were

among people over 60 years of age. The mortality of massive hemorrhage increases greatly with age.

Sex. Sex has a definite influence on the prognosis. Before the turn of the century peptic ulcer was generally considered to be more common in the female sex. The vital statistics for 1953 show that less than 20 per cent of the total number of ulcer deaths occurred in the female sex. In England and Wales (1947), only 22 per cent of the ulcer deaths occurred in the female sex. These figures imply that in the female sex, ulcer is less common and it is a less severe disease. Fewer females than males require surgical treatment for complications.

Significance of Past Medical History. Data are needed on the relationship between the past medical history and the prognosis of the patient with peptic ulcer disease. In other words, is a patient who has had attacks of peptic ulcer disease for eighteen years a worse risk at the age of 48 than the person of the same age who had his first attack this year or last year? It must be assumed that he is a less desirable risk but, oddly enough, nobody has gathered adequate statistics bearing on this relationship. Indeed, we do not even know precisely what effect the "frequency of recurrences" and the "duration of each previous attack" has on the prognosis in peptic ulcer disease. It is suspected that peptic ulcer patients who have had very frequent attacks and whose episodes of ulcer activity last twice as long as the average will be more likely to develop complications earlier in the course of the disease.

Local Milieu. Turning to the local milieu and prognosis of peptic ulcer, what effect does the *gastric acid* have? Suppose, for example, a hundred patients have gastric acidity of 100 free units of HCl and another hundred patients have 50 units; what difference will be noted? There is reason to believe it very likely that the patients with hypersecretion and grade IV acidity have a poorer prognosis, both from the standpoint of recurrence and from the standpoint of the development of complications. Unfortunately, at this time we do not have sufficiently accurate statistics to evaluate the risk of the ulcer patient with 100 units of free acid as compared with the risk (recurrence and complication) of the patient with normal or reduced acidity.

The influence of concomitant gastritis on the prognosis of peptic ulcer disease has not been clearly established. It is believed that a patient with peptic ulcer who has advanced erosive or hypertrophic gastritis is a poorer risk from every angle than the one without this complication.

Ulcer Cicatrix. What the degree of duodenal scarring seen by x-ray means from the standpoint of morbidity, is not known. A grade IV cicatrix is not a good thing for the duodenal ulcer patient as he is more likely to develop obstruction, more likely to bleed, and more likely to require operation. Unfortunately, statistics are not available to bear this out. Indeed, there are many factors bearing on prognosis which have not been accurately appraised. It would seem to be nearly time some one started to find out what the facts are and thus end the guessing.

Gastric Ulcer vs. Gastric Malignancy. The effect of *"erroneous diagnosis"* on the prognosis is tremendously important. Everyone knows that no good clinician can be right every time when he says that this ulcer is benign and that one is malignant. Everyone knows that it is not good policy to operate on every patient who is a bad risk just because he has a gastric ulcer when there may be only a 10 per cent chance that it is malignant.

The following definite plan is suggested for these patients. It is a very rigid ritual. If there is nothing about the lesion (roentgenoscopically) or its local milieu (subtraction defect, achlorhydria) to suggest the presence of a neoplasm, they are put on the physiological stomach rest regimen. They receive hourly feedings of milk (135-150 cc.) and hourly doses of antiacids for ten to twelve days, and then x-ray examination is repeated. If there is not tremendous improvement in the character of the lesion in this brief period, they are then operated upon. If this plan were followed routinely, instead of relying principally on the degree of acidity, the size of the ulcer fleck, the presence or absence of malignant cells by intubation technics and gastroscopy, fewer mistakes would be made.

If every patient with gastric ulcer is operated upon, a number in the old age group will succumb who otherwise would have responded to medical management. On the other hand, patients

die by neglecting to follow a brief therapeutic ritual and by postponing operation unduly when malignancy cannot be satisfactorily ruled out. It is readily seen how this situation affects the prognosis.

Ulcer Complications. This, of course, is about the most important aspect of prognosis because most such patients do not die of uncomplicated peptic ulcer. They die either of complications or as a result of poor management or of concomitant disease. About 10 per cent of ulcer patients who come to the office of the doctor who is interested in gastroenterology, have or will have, complications of peptic ulcer disease; 40 per cent of those who go into a general city hospital in this area with peptic ulcer will have a complication when they arrive. There is a big difference in these two groups — those who are seen by the doctors in the outpatient department and those who are admitted to the hospital.

The important complications that have something to do with hospital admission are massive hemorrhage, free perforation, and obstruction. Edwards and Jennings analyzed 586 consecutive admissions for peptic ulcer in a large general hospital. Twenty-three per cent were admitted because of hemorrhage; 14 per cent because of free perforation; and only 3 per cent came in with obstruction. Why the complication of duodenal stenosis seems so much less now than formerly is not understood.

From Oslo there is another breakdown available of the relative frequency of hemorrhage and perforation in peptic ulcer disease. *After the age of 60 years*: 72 consecutive patients were admitted to a general hospital with ulcer complications and died. Forty-nine died from massive hemorrhage and 23 deaths were from perforation — twice as many deaths from hemorrhage as from perforation. *Under the age of 60 years*: 45 patients were admitted and died, 17 from hemorrhage and 28 from perforation. Twice as many deaths were from perforation under the age 60 years and twice as many deaths were from hemorrhage after the age 60 years indicating, again, how important the age factor is.

Massive Hemorrhage. What are some of the facts about hemorrhage, probably the most frequent cause of death among

the complications? A good many of these deaths are attributed to cerebrovascular accidents, myocardial failure and other causes, but it is the hemorrhage that sets up the chain of events. The overall mortality of truly *massive* hemorrhage, based upon hospital statistics in this country, is in the neighborhood of 10 per cent if all ages are included. In a recent series reported by Rosenak, 223 consecutive admissions showed a mortality of 13.4 per cent from massive hemorrhage.

Actually the precise figure for the *occurrence* of massive hemorrhage in peptic ulcer disease is not known, because it is not known what percentage of people with peptic ulcer disease ever get into a hospital. It is known that of the patients entering a hospital for ulcer disease over 20 per cent will be there because of massive hemorrhage. If they are there for that reason, about 10 per cent of those who come in with massive hemorrhage will die there.

Mortality statistics have been carefully studied on an age basis. Mass statistics have been gathered by Crohn and by Ivy. Under age 40 the mortality for massive hemorrhage is 4.3 per cent; over age 50 it is 15.4 per cent; over 60 it is 21 per cent. In this country the mortality from massive hemorrhage is almost twice as great in the male as compared with the female sex. Mentioned previously was the influence of ulcer *site* upon occurrence of hemorrhage. A number of different investigators report the mortality from hemorrhage of gastric ulcer to be from two to four times greater than that from duodenal ulcer hemorrhage. A higher mortality from hemorrhage is to be anticipated in postbulbar than in bulboduodenal ulcer.

Of the patients who die of massive hemorrhage, 80 per cent are known to have had hematemesis. In other words, a patient who has a massive hemorrhage from peptic ulcer and who vomits blood has less chance of surviving than a patient who has bleeding from an ulcer and only melena. Indeed, if he has a massive hematemesis and is over the age of 50 and it is the first hemorrhage with peptic ulcer disease for many years, the anticipated mortality is in the neighborhood of 30 per cent.

The *first* hemorrhage in chronic ulcer disease involves a much higher mortality than any subsequent one. Indeed, the more

hemorrhages a person has, the greater chance for survival from the next one. If the local milieu in the ulcer patient encouraged failure of clot formation and of vascular contraction, the first hemorrhage may very well prove fatal. This is precisely what happens in the elderly patient with arteriosclerosis and a marked ulcer cicatrix.

Ordinarily ulcer pain subsides with the occurrence of bleeding. If a person comes in with a massive hemorrhage and the pain of the ulcer in that attack does not subside, the course is likely to be a troublesome one. There is a good chance that the patient will need operation while he is bleeding. Unfortunately, accurate figures are not available dealing with the prognosis in the patient who continues to have ulcer pain after the occurrence of massive hemorrhage. A bad prognosis may be anticipated if a patient admitted with massive hemorrhage stops bleeding, but bleeds massively again after a few days. If immediate operation is not done, the mortality may approximate 50 per cent. The prognosis on conservative medical management is also poor with the onset of massive bleeding in the hospitalized patient who is on a strict ulcer regimen, and who has never bled before. In most instances of this sort, immediate operation affords the best chance of survival.

The association of vomiting with massive hemorrhage increases the mortality. There are two reasons for this. A satisfactory clot may not get a chance to form. Secondly, a number of these patients have gastric uremia, that is, hyperazotemia, alkalosis and a hypochloremia, before they start to bleed because of loss of hydrochloric acid in the emesis. The onset of bleeding increases the dehydration and impairment of renal function may become severe.

Free Perforation. Obviously this complication plays a significant role in ulcer prognosis. In similar age groups, the mortality from free perforation in the large city hospitals in this country is somewhat less than the mortality to be anticipated from massive hemorrhage. An average mortality for free perforation at all ages is approximately 8 per cent, whereas the mortality from massive hemorrhage approximates 10 per cent. The mortality for perforated gastric ulcer is about twice as great as that of a free perforation of a duodenal ulcer.

Pyloric Obstruction. This is not as important as it once was among the complications of peptic ulcer. Statistics of twenty years ago show an incidence of pyloric or duodenal obstruction of approximately 20 per cent in autopsies on patients who died because of peptic ulcer disease in this country and in England. At the present time, the incidence of this complication is much less, for reasons that are not yet understood. The principal effect of pyloric and duodenal stenosis upon the prognosis at the present time is only the mortality that one would anticipate from an operation of election, if the patient is in expert hands. In other words, if the patient is well prepared for operation, the mortality risk from operation will not exceed very much that of any other complication and will actually be less than some.

Generalizations Concerning Influence of Complications. What about the remote influence of complications on prognosis in peptic ulcer disease? As examples, individuals with peptic ulcer may have had a bout of hematemesis last year, three bouts of melena, a free perforation four years ago, or a study two years ago revealing evidences of pyloric obstruction associated with vomiting. What effect do these complications have on the frequency of recurrence of peptic ulcer and upon the occurrence of further complications?

One may conclude that generally any of these complications developing in the course of peptic ulcer disease will cause an increase in the incidence of recurrence; they will increase the incidence of other complications and they will increase the incidence of future need for surgery. It is evident, therefore, that if one segregates cases of peptic ulcer with a history of one of these three serious complications, and compares them with another group of cases in which there was no history of complications, the group of patients who have survived complications will be more susceptible to recurrences, to the development of additional complications, and to the need for future surgery. This also applies to the patient who has had gastric stasis or gastric retention. It probably applies particularly to the patient who gives a history of massive hemorrhage. Unfortunately, satisfactory statistics are not yet available on the exact incidence of ulcer recurrence and of ulcer complica-

tion in the patient who has experienced massive bleeding, as compared with the ulcer patient who has not bled.

We know a little more about those with the history of perforation. A follow-up of from a year and a half to twelve years, carried out by O'Malley and Drury (Dublin, 1953) on patients having had a simple closure for free perforation, disclosed that 50 per cent experienced either a serious complication or required further surgery during this interval. In Kingbury's series of 170 patients who had suture operations for a perforated ulcer (mortality 10 per cent), 30.7 per cent of survivors required further surgery during a five-year follow-up. A history of free perforation means that one is justified in putting the patient into the category of an ulcer diathesis, anticipating a good likelihood of further ulcer troubles.

Intractability. Intractability means inability to relieve symptoms or lack of successful cure. When one speaks of curing an ulcer, it should be done with two phases in mind. What is meant — healing a particular ulcer, or bringing about a cure of ulcer disease? There is a great difference. Treatment results in great success with the healing of an uncomplicated ulcer. Over 90 per cent will heal on a good physiological stomach-rest regime. On the other hand, rather poor success is experienced in bringing about a permanent cure of peptic ulcer disease by medical means. Between 50 and 70 per cent of patients will have had a recurrence within two years.

These two facets will be discussed separately. First, what accounts for inability to heal an individual ulcer? This is an indication of intractability. In some instances, this is the fault of the physician. It may be the result of injudicious therapy or, rather, the lack of therapy. In my opinion, it is often due to placing too much reliance on drugs (particularly anticholinergic drugs) and giving too little attention to physiological stomach rest. The latter is accomplished by deletion of meals as such and the institution of small liquid hourly feedings (mild) with between feeding hourly doses of antacids. This has more value in the healing of any individual uncomplicated ulcer than any drug. Unfortunately, too often the anticholinergic drug does bring about symptomatic

relief, but the stomach is not being rested on an hourly feeding diet and ulcer healing does not occur.

Another responsibility for intractability is that of the patient. He may fail to see a physician early in the course of a recurrence, because the ulcer distress often is not too annoying at first. The average person does not pay much attention to the mild gnawing or aching discomfort until one, two or three weeks have elapsed. Then there are a number of patients who will not adhere to a strict regimen, and others who cannot do it because of psychological or environmental factors. A third reason for intractability — and this is very important — is the lack of recognition of a complication.

There is one complication that does not fit into any of the categories mentioned so far. Sixty-five per cent of elective operations at the Graduate Hospital were not performed for hemorrhage, free perforation, or obstruction. They were performed for intractability due to a confined perforation, that is, a perforation which had never been free but the ulcer had attached itself to a surrounding structure, or had penetrated deeply into that structure. For example, a walled-off ulcer may perforate into the pancreas. That accounts for the inability to relieve symptoms in a great number of patients, in whom the intractability is not due to inadequate physician care or inability to follow a regimen on the part of the patient.

The failure to bring about a permanent *cure of the disease* is a different matter. This often is due to the nature or life history of the disease, and there is not much that can be done about that in many instances. However, physicians are guilty at times of not instructing patients about the prevention of recurrences. They may not be able to prevent recurrences in many instances, but it is known that fewer recurrences result if the patient learns to take a small in-between-meal feeding (preferably milk) indefinitely, instead of allowing the stomach to remain empty for four or five hours. There are fewer recurrences if some of the nervous tension and emotional factors are controlled and some effort made to correct the bad habits. Patients should be instructed what to do in the event of a respiratory infection and what drugs (aspirin, for example) to avoid. Patients should be instructed about the

dangers of certain drugs that are now valuable in the treatment of other diseases. Iatrogenic implications exist here, as they do in almost every other field of medicine. I refer to steroid therapy, some of the newer antirheumatic remedies (Butazolidin®) and the use of aspirin. All three of these drugs have a deleterious effect on the stomach in many ulcer patients and their use should be avoided if at all possible.

Prognosis may be adversely affected also by inadequate institution of immediate care for recurrences. So many people with peptic ulcer have never been told what to do when the next attack comes (which it will in over 50 per cent of patients) and the advice is very simple. With the advent of the pain of recurrent ulcer, the patient should stop eating meals at once. If all would begin hourly milk feedings, 75 per cent of them would experience relief of pain with that attack at the end of 24 or 48 hours. Yet, how many patients with ulcer are actually told about the importance of early recognition of the telltale, late after-meal distress, which is relieved by eating, and which, in so many instances, can be so easily corrected?

It is not known, actually, how many complications occur because patients had not received proper instructions concerning the prevention of recurrences. Peptic ulcer disease often gives rise to very mild symptoms in recurrent attacks for many years prior to the occurrence of a complication. The conception that every peptic ulcer is serious is unjustified. As a matter of fact, many people who get nasal allergy every year are much more miserable than many peptic ulcer patients who experience a duodenal ulcer attack each year, but who control their distress within 24 or 48 hours with an hourly feeding regimen.

Peptic Ulcer Surgery. In my opinion, 60 per cent of the complications requiring operation in peptic ulcer disease occur in people who have a very long history of recurrences and a history of inadequate care of their recurrences. This figure is reasonably accurate and that is the reason for stressing the importance of attention to the ulcer symptoms when they develop and not three or four weeks later.

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Bockus, Roth and Haubrich have reported the experience with Billroth II type of operations at the Graduate Hospital. The mortality was 2.1 per cent in 188 consecutive operations performed for peptic ulcer. It can be said that radical, subtotal resection, performed by an expert for peptic ulcer disease, should not entail a mortality above 2.5 per cent. For the purpose of determining ulcer recurrence rate, we have reviewed records on 262 patients who had subtotal resections, with a follow-up of from three to twelve years. Recurrence of ulcer was experienced by only 2.3 per cent. That means six recurrences in 262 patients, followed for an average of 4.6 years. Of those six recurrences, five patients had had resection of two-thirds or less of the stomach. Only one recurrence developed when the resection had removed three-quarters or more of the stomach. Why then, is a three-quarter or more resection not always done? This is a good operation. Only two per cent die, and two or two and a half per cent will get a recurrence. Unfortunately, there are another 5 to 10 per cent of patients who are not going to do so well with a subtotal resection, and that is where the difficulty lies. They will have side effects that are unpleasant. They may experience after-meal dumping or they may be unable to maintain normal nutrition, either one or both. We are trying now to devise means of prognosticating which patients requiring ulcer surgery may develop disagreeable *side* effects. If this can be done, some operation other than Billroth II type of subtotal resection should be selected for these "reactors." As a result of a recent analysis of material (Roth, Becker, Vine and Bockus) it is suggested that disagreeable side effects of subtotal resection are most often encountered in the female sex, among allergic people, among patients with labile autonomic nervous systems, in those with hypersensitive vasomotor systems and in those who may be labeled "neurotic." Most patients of normal weight who do not belong in any of the above categories will tolerate a three-quarter resection perfectly well. In summarizing our experience with three-quarter resections, operating without careful selection from the standpoint of reactivity, there are approximately 85 to 90 per cent with good results, that is, two per cent mortality, two to two and a half per cent recurrence, 5 to 10 per cent with very disagreeable side effects.

The prognosis of peptic ulcer disease is probably influenced more than most other diseases by the degree of expertness of the medical care received, for in many instances the recurrences are mild and will remain so if they are treated properly.

The complications which affect the mortality and which result in operations could be reduced considerably if we had a better dissemination of knowledge concerning the proper meticulous care of recurrences.

There is, likewise, great need for a more accurate statistical appraisal of many of the aspects of this disease. It is hoped that money may be made available to further much needed research in this field.

These are the concluding remarks of the Hunterian Lecture, delivered in 1932 by the late Dr. John Ryle, who was Regis Professor of Medicine at Cambridge University. Let us see how true they are in 1955.

> "All surgeons and physicians who undertake the treatment of this troublesome disease must endeavor to preserve the studious attitude, not lightly accepting opinion or submitting to the bias of their craft, and remembering always that they are not, in fact, concerned with peptic ulcer (the lesion) but with peptic ulcer, the disease, as it occurs and as it varies in individuals of special type and temper and differing daily circumstance. In each case, briefly, judgment must be passed, not upon the presence of an ulcer alone, but upon a proper understanding of the whole patient and the whole disease.
>
> Peptic ulcer has general effects on the body and the mind as well as general causes in them, and no effect or cause can be neglected. It is, I believe, a just criticism of surgery and medicine in the present era that they have concentrated on parts to the exclusion of the whole, and on technique to the exclusion of philosophy. In peptic ulcer, no less than in many other maladies, we have come to rely on too narrow a pathology. In our therapeutic quest, we have been too little observant of physiological principle. We are all compelled by the magnitude of our subject to be something of specialists, but this should not necessitate an abandonment of that naturalistic outlook which marked the achievement of our old preceptors, from Hippocrates to Hunter."

This English physician has expressed in a few sentences the epitome of what ulcer management ought to be.

DR. RICHARD S. GUBNER — Dr. Bockus, some cardiologists feel that gastroenterologists are helping in an iatrogenic way actually to cause coronary disease by the prescription of high milk and high fat diets in peptic ulcer. There have been one or two such series reported in the literature, and most physicians seeing

many patients with coronary disease have encountered patients with a background of peptic ulcer who have been on a high milk, high fat diet.

I should like to ask you to comment on that, but, first, I should like to ask two other things.

To even up the score of what gastroenterologists are doing to the heart, I wonder whether, in your experience, you have seen any ill effects from the cardiologists' employment of reserpine products, in causing or aggravating peptic ulcer? Reserpine has recently been shown to have a powerful, stimulating effect on gastric acid. I have seen one fatal hemorrhage, in a hypertensive person, otherwise previously well, who was on reserpine.

One further question that I would like to put to you is that recently, in England, there have been studies recommending the medical treatment of acute perforating peptic ulcer, and in this country there has been one extensive study, showing a very low mortality with acute perforation. I wonder what your outlook or what your view is on this procedure, using antibiotics, intubation, and strict rest, as compared with ligation, particularly in view of the fact that you commented that simple suture so often leads to subsequent complications.

DR. BOCKUS — I would like to discuss this interrelationship between the cardiologist and the gastroenterologist in a number of different facets, touching on one or two which the interrogator did not mention. I think that there ought to be a little closer liaison. We are trying to establish that in Philadelphia. That is one of the things that Dr. Ryle stressed — too much knowledge about too little, and not remembering about the other systems that are related.

Do you know how many gastrointestinal patients I have seen resulting from the practice of many cardiologists of prescribing from one to two ounces of whiskey, three times a day, before meals and before retiring, because the patient had had an anginal attack? Quite a few, and it is a bad practice for patients who have gastritis, peptic ulcer, liver or pancreatic disease. Many of these people had never tasted alcohol in their lives. Imagine getting up in the morning and taking one or two ounces of

whiskey without ever having had it before. This acts as a vigorous stimulant of gastric secretion and irritant to the gastric mucosa.

I should like to mention particularly the practice of many physicians and cardiologists who, by their atitude or discussion, create a state of anxiety in patients with heart disease or heart pain. I see many functional disorders of the alimentary tract and at times a flareup of some organic disease because of anxiety, at times iatrogenic, following knowledge or fear of heart disease. Approximately 50 per cent of patients, after a myocardial infarction, coronary thrombosis, or the establishment of angina on effort, develop an overlay of gastric symptoms. This is due ordinarily to aerophagy as the result of anxiety based on the fright and fear of heart disease. Cardiologists should keep in mind these iatrogenic disorders.

There is no need to prescribe a high fat diet in the patient with peptic ulcer. If one is dealing with a patient in the susceptible age group or one who already has cardiovascular disease, the ulcer diet can easily be arranged without fat. Similar modifications of the ulcer diet are often required in patients who have concomitant gallbladder disease and who are obese. During active ulcer treatment they may have hourly feedings of skim milk. One can increase the neutralizing as well as the caloric value of the mixture by adding a skim milk powder. With a little additional nonabsorbable antacid between meals the regimen is quite satisfactory for active ulcer treatment.

The need for low fat diet is frequent in peptic ulcer patients, not only from the cardiovascular angle, but because many patients with peptic ulcer are overweight, and quite a few have gallbladder disease. There are others with liver disease, to whom I don't like to give too much fat.

Pincus, in our clinic, is studying the effect of serpasil and reserpine on gastric secretion, at the present time. I think there is little doubt but that they have a stimulating effect on gastric secretion. I do not know what the effect on pepsin is.

With regard to medical treatment of acute perforation, that is, of course, a very important and interesting question, and what you say is entirely true. It has been amazing to most of us, how

many of these patients with a free perforation survive with medical management.

In summarizing the papers that were in the literature up until two years ago, it was found that only eight and nine-tenths per cent succumbed as a result of the medical management. Now, as mentioned a moment ago, simple suture of a free perforation entailed a mortality of not much under eight per cent. Of course, there are reports of a much lower mortality — in the neighborhood of two or three per cent. Actually, in mass statistics, the mortality rates of medical and of surgical treatment are not very far apart.

There are certain disadvantages to medical treatment. In the first place, the risk of operating in the event of free perforation under six hours duration in a patient not otherwise a bad risk, is so low that it is best to operate. One never knows which of these perforations is not going to seal off properly. The incidence of subphrenic abscess and perihepatic abscess will be greater under medical management.

We ought to continue operating on patients considered to be good operative risks if they are seen early. Medical management may be tried in patients who are seen late and those who are poor risks for other reasons, including advanced cardiovascular disease. This means gastric intubation with constant suction. Close supervision is required to make sure that the tube stays in the dependent part of the stomach so that all or most of the gastric juice can be aspirated. Antibiotics, pain-relieving drugs, and parenteral feedings are required.

Of course, some will develop a perforation where surgery cannot be performed. At sea and in out of the way places a gastric tube and syringe may well be life-saving.

Dr. R. C. Montgomery — Dr. Bockus, you mentioned the dumping syndrome. Would you say a word more about that? Does time tend to cure those individuals?

Dr. Bockus — Somewhere between 25 and 50 per cent of our patients who have a three-quarter resection will develop mild, early, after-meal symptoms. This may be nothing more than fullness. Nausea is another rather common complaint. Often, in the reactive person, there will be, in addition, sweating, tachy-

cardia, palpitation, something simulating syncope or dizziness, and sometimes a loose bowel movement. The patient who has all of these is rather miserable. Dumping is present frequently, but is very, very mild in a great many patients. We have a number of patients who never admitted having dumping, until they were asked specific questions. It comes on in many patients when they first start to take meals as such. After the operation, on the fifth or sixth day, the surgeon often changes the diet from frequent liquid feedings to little meals with three or four things. With these early meals, particularly if they include milk or cereal or porridge, many patients will experience dumping. Many soon learn to eat less for a time and dumping never proves very troublesome. But there are about 5 or 10 per cent of patients who will continue with symptoms after meals for a long, long time. They may be very miserable and meticulous treatment is essential.

In the first place, their diet has to be carefully arranged and in most instances it must be dry. They should not have any liquids at all with their meals. Secondly, they do very much better without milk at any time. Many of them do better without porridges and sweets at mealtime. Often they can take them between meals. Frequently, a strong anticholinergic drug 15 to 20 minutes before meals is helpful. They should be instructed to stop eating when they get the disagreeable sensation and to recline for a few minutes until the sensation has passed.

We have perhaps three or five per cent of these patients who continue to be so miserable that they cannot carry on ordinary activities. With many "bad dumpers", one may often experience some improvement after an interval of six months to two years. As time goes on, most of them learn to live with the disability. Unfortunately people who have severe dumping for a long period usually develop undernutrition. Sitophobia occurs and they will never again resume eating anything like the amount of food they require and gradually they lose a great deal of weight. After they lose twenty or thirty pounds, the weight may remain stationary. They unquestionably slow up physically so that energy requirements are low. They may be eating only one-half the amount of food which they were in the habit of eating prior to their stomach trouble. Some of them go along in that fashion for years.

PRESIDENT WILLIS — Thank you, Dr. Bockus. We appreciate the time you have given us and your splendid paper on the prognosis in peptic ulcer disease. As I mentioned earlier, your subject is very important to us, and there is no one whose opinion we would rather have on the prognosis of this disease. Thank you again.

Until a relatively few years ago, perhaps thirteen or fourteen, people with diabetes mellitus were not considered insurable. At about that time, a few companies started underwriting these risks, and now, almost all companies will issue insurance to people with diabetes. At first, the selection of these risks was very rigid, but it has gradually become more liberal. However, we are still uncertain whether or not we are properly classifying these cases. I am sure that the next speaker will help us on this subject, which is, "The Altered Prognosis in Diabetes Mellitus." The speaker, Dr. Herbert Pollack, is Associate Professor of Clinical Medicine, New York University College of Medicine, Attending Physician, Bellevue Hospital, and Physician for Metabolic Diseases at Mount Sinai Hospital in New York. It is a pleasure to present Dr. Pollack.

THE ALTERED PROGNOSIS IN DIABETES MELLITUS

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The discipline of medical schools and of medical teaching over a period of time has been one of observance of *traditional authority*. We are taught certain things in medical school by the professor, and what he said was gospel. Sometimes, we fail to think the subject out a little more clearly and logically, being willing to accept what we were told.

That has occurred in the field of diabetes, perhaps to a greater extent than in other branches of clinical medicine, because diabetes today is still poorly understood. The problems concerning the disease are several. First of all, what is diabetes? What are the diagnostic criteria, and how do we know when a patient has diabetes? The current concept or the current definition of diabetes mellitus is an elevated blood sugar level and glycosuria. That does not necessarily mean diabetes mellitus, as we know, even though that is our definition.

The mere fact that a patient has certain changes in his blood sugar concentration should not lead one to make an irrevocable diagnosis of diabetes. Once such a label is given a patient he is marked for the rest of his life. If the criteria are accepted as set up by the American Diabetes Association for normal blood sugar levels, either during fasting or after eating, using the venous, or capillary blood methods, for the true blood sugar, or the total reducing substances in the blood, there will be wide variations in the blood sugar concentrations. They start at 110 mg. for the fasting venous blood, using the true blood sugar methods, and go up to 240 mg. after eating, by the capillary methods. Concentrations greater than those are considered as diagnostic of diabetes mellitus; lower concentrations are considered to be nondiabetic.

Obviously, we must add one more criterion to blood sugar levels. That is, whether the elevation is irreversible or permanent,

because it is not at all uncommon to see blood sugar concentrations of this type in people who never had diabetes and never will have it, due to certain circumstances occurring at the moment the specimen of blood is taken. If one studies the blood sugar concentrations, for instance, in children with the exanthematous diseases, it will be found that over 33 per cent of these children will show what is now called a diabetic type of glucose tolerance curve. Yet, three weeks after recovery from the exanthematous disease the glucose tolerance curve returns to normal. Not infrequently the glucose tolerance in people who have had fractures of the long bones resulting from trauma is of typical diabetic type, which will persist for as long as six to eight and sometimes ten weeks. Then the glucose tolerance curve reverts back to a perfectly normal status.

Now, are these people diabetic, even though they have glucose tolerance curves that satisfy all the criteria which our most rigid disciplinarians have taught us to look for in this diagnostic procedure? It is my opinion that these people are not diabetics, and these transient interferences with carbohydrate or protein metabolism — which is what they are essentially — have no basic influence on the overall picture of longevity or good health. The diagnostic criteria used today for establishing the diagnosis of diabetes should be carefully reviewed. Then, is diabetes a disease? Is it a disease entity — once the diagnosis is established? Again, there is the question of whether this traditional concept can be accepted any more.

It is my belief that diabetes, as seen clinically, is actually a clinical syndrome, the origin of which is quite varied, because one can see the diabetic syndrome originating from liver disease, pituitary or adrenal disease, pancreatic disturbance, or from purely peripheral mechanisms, whereby there has been no interference or neutralization of insulin. However, the block is in the peripheral end of the enzyme systems, which prevents insulin from exerting its full activity on that phase of the carbohydrate cycle. A block anywhere along the line, whether it is in the deposition of glycogen, in the transference of glucose to fat, in the oxidation of carbohydrate or in the interconversion of protein to carbohydrate and back again will give identically the same

end syndrome and that is elevated blood sugar concentration and the resultant glycosuria.

Therefore, a search must begin for the diagnostic criteria which will permit localization of the type of diabetes, or the origin of that particular diabetic syndrome. It is my belief that longevity of the patient is related to the origin of this syndrome, rather than to the syndrome itself, for some of the syndromes are associated with accelerated atherosclerosis and vascular phenomena, and some are not, as we will point out in a few moments.

The next point is the question of objectives in the treatment of diabetes today. Before the introduction of insulin there was only one objective in therapy, and that was to keep the patient alive as long as possible. Then, when regular insulin was introduced, the objective of therapy was to keep him alive somewhat longer. Again, there was no attempt made to restore these people to a normal physiological basis. However, today the criteria, fortunately, are entirely different. Our objectives and our therapy today are to restore these patients to as full an active life as is possible. That is why children are taught, when we can get them away from overprotective parents, to have a little more freedom, exercise, activity, and a full nutritionally adequate diet with control of the glycosuria. Over the course of years, therefore, from 1921 through 1954, or today, objectives in therapy have changed. We are no longer worried about merely maintenance or survival. Now, we are interested in the restoration of a normal metabolic picture as completely as may be possible.

One of the difficulties in approaching the problem is the proper classification of diabetes as seen clinically. All too frequently the house officer in presenting a case says, "This is a mild diabetic, he requires no insulin but he is losing his right leg from arteriosclerotic gangrene, and he has lost the sight of both eyes because of retinitis." It is regarded as a mild case, because the insulin requirements are low. Then, presenting another patient he says, "Here is a very severe diabetic. He requires 90 or 100 units of insulin a day, but on complete examination, there are no stigmata of deterioration." He is classified as severe because he takes insulin.

The question remains, what are going to be our criteria for the severity of diabetes? Merely the amount of insulin which is re-

quired to control only one phase of this diabetic syndrome, that is, the glycosuria? Or, is the severity to be established on the basis of the deterioration of the individual and the threat to his longevity and health, and by the associated degenerative processes which occur in a group of diabetic persons? I leave the answer to you. I have my own answer and my own opinions. I believe that we must re-establish the criteria that we want to use in discussing severity of the diabetic syndrome as we see it clinically.

What is the big difference in the outlook in diabetes today, and what was the major event that brought about this difference? We do not have to look any further than one situation which has altered, and that is the types of insulin now available.

The original insulin, the water-soluble extract, had a sort of explosive action. It was injected and, within thirty to forty minutes at the most, it exerted its effect. By the end of four hours the activity was over. The patient who required large doses of insulin, anything over 20 or 30 units a day in the original insulin days, was under control only about eight to nine hours a day, and was without control for the rest of the day. The word control is not necessarily used in reference to glycosuria or limitation of glycosuria. It refers to the secondary metabolic effects which are associated commonly with glycosuria and are the catabolic protein effect, or the nitrogen losses. In our patients with experimental ketosis it was demonstrated that the use of regular insulin did not allow for nitrogen retention during the tweny-four hour period of a day. It may be recalled in the early days of insulin use, between 1921 and 1935, these patients frequently had ketosis in the morning when they awoke. These were the patients who required four doses of regular insulin a day, one before each meal and another one at bedtime, and frequently they had to be awakened for a dose during the night.

Prebreakfast glycosuria was very common, of course, because the insulin taken at the evening meal had worn off long before midnight. During the period of time from midnight until breakfast there was no metabolic control and they were losing nitrogen by exhausting the protein reserves in the body. With the introduction of the so-called long-acting insulins this picture was completely reversed. The first of these was protamine zinc insulin,

which became available about 1935 or 1936 and clinically its extensive use was started about 1937.

During periods of intensive glycosuria and mild ketosis, the patient is in negative nitrogen balance, negative riboflavin balance and there is interference with the nicotinamide or the niacin as well as with the whole enzyme system, which produces many of the degenerative effects in diabetes. These patients on regular insulin who would develop ketosis in the morning were the ones who showed the marked degrees of deterioration and nutritional degradations, quite commonly.

Protamine zinc insulin altered that picture although it was a very difficult insulin to use. We got into a great deal of trouble with it because, again, this traditional thinking of physicians guides us into the habit of doing things a certain way, and we forget that when the conditions change we must also change our thinking.

The dietary factors in the treatment of diabetes had been established in the preinsulin days. Starvation therapy was employed because by starvation a patient could be kept alive much longer than by allowing him to eat a nutritionally adequate diet. Consequently, starvation was looked upon as a way of saving the diabetic. With the introduction of the regular insulins starvation was continued as the optimum dietetic therapy, because the regular insulins had practically no influence except for the maintenance of survival. They did not restore the metabolic balances to normal, as we have just pointed out.

Then, when the long-acting insulins became available, physicians were so accustomed to prescribing certain types of diets that they continued their use, failing to recognize that the long-acting insulins had an entirely different physiological action as compared to the short-acting ones. Consequently, we had trouble with nocturnal hypoglycemia.

Obviously, the thing that compounded the error was, again, our traditional hospital practice. The first patients with protamine zinc insulin were handled in our best hospitals as bed patients because we were afraid of it. It was soon apparent that it did have a 24-hour activity and, in some patients, even a 36-hour activity.

But we failed to coordinate the hospital medical management system.

Our hospitals, as you know, usually give a patient early breakfast. He is awakened at five-thirty o'clock in the morning for a bath, and then they give him breakfast at seven. Then he gets luncheon at eleven and his evening meal at four or four-thirty. Then, from four-thirty in the afternoon to seven o'clock the next morning, the patient gets no food.

When a type of insulin is introduced having a 24-hour range of activity, it does not know that the kitchen staff has to go home at four-thirty or five o'clock. It just continues acting. In the early days of protamine zinc insulin, it was very difficult to wake up some of these patients in the morning. They were actually in a state of severe hypoglycemia. That discouraged many physicians from taking full advantage of the metabolic possibilities in long-acting insulins, because the immediate clinical problem of severe hypoglycemia and the vascular accidents that occurred during the hypoglycemia, they thought, counterbalanced the benefit of the new insulin.

It required a good deal of experimentation with types of diets and recognition of physiological activities, study of the physiological activity of the gastrointestinal tract and the carbohydrate values available from foods, before we arrived at the present type of dietary regime, introduced some years ago. That is to say, we began to use the high protein evening meal, because the protein is converted to carbohydrate very slowly, and a half pound of steak is equivalent to a constant intravenous injection of glucose over a period of eight hours. By altering the diets to that extent, we were able to combat nocturnal hypoglycemia, and use the long-acting insulins with a good deal more effectiveness.

What has happened since the introduction of these long-acting insulins? Prior to 1937, the mortality rate among diabetic patients with the complication of infection was 38 per cent in a study of 500 successive hospital admissions to Mount Sinai Hospital, New York, and 150 autopsies. Something over 60 per cent of the patients admitted to the hospital with diabetes were admitted because of infections producing some evidence of ketosis. We did not admit those with respiratory infections at all, but infections

serious enough to produce ketosis accounted for over half the admissions of all diabetic patients prior to 1937. The cause of death was cardiovascular disease in 48.6 per cent of those dying in the group.

Since the introduction of the long-acting insulin, one carbuncle has been observed in a patient under therapy in my practice. A few have been seen in patients admitted to the hospital who never knew they had diabetes. One patient who had been under therapy since 1938 also had a carbuncle. That is a remarkable change over the years.

As you will recall, carbuncles were practically the fraternal sign of a diabetic person in the old days. If there was a big cruciate scar on the neck, it was a sign that the person had diabetes, and practically every person with diabetes had one. It was the most common type of infection and its incidence has completely disappeared. This is very largely due to the fact that the long-acting insulins enable these people to stay in positive nitrogen balance, under all situations of dietary abuse. The positive nitrogen balance allows them to build up their immune bodies, and develop an effective resistance to infections.

That is what is meant by the altered prognosis and the altered situation in diabetes. Now, what can be done to take advantage of this situation?

There is a dictum that good health is dependent upon optimum nutrition. Resistance to infection is dependent upon optimum nutrition. Therefore, it occurred to me to analyze the diets that are being prescribed for diabetic patients around the country. A mail questionnaire was made up and sent out to over 70 of the key hospitals in this country, asking them for copies of their diet lists used for distribution to diabetic patients. The total daily intake being prescribed for diabetic patients around the country varied from about 1640 to 2100 calories. In one of our major New York hospitals the diabetic diets being prescribed varied from 1400 to 2000 calories. Schenectady Hospital sent sheets of their diets which varied from 1000 to 1880 calories, with a notation that they very seldom prescribed 1880 because the carbohydrates were over 150 grams.

The American Diabetes Association put out a manual of instructions, and the diets ran from 1200 to 2200 calories for adults and from 1800 to 2600 for children. People adopted these without reading the fine print that went with the table which said, "Please use this only as a basis for calculation, and add as much of the fats as is indicated to bring the calories up to requirements." But they failed to do that, instead, they took the tables literally, resulting in a flood of American Diabetic Association diets throughout the country which did not meet even the minimum standards adequate for nutrition, much less being entitled to carry the authenticity of this major organization which is interested in diabetes.

The Food and Nutrition Board of the National Research Council has set up requirements or recommended allowances for caloric expenditures of people, and the vigorous male adult, in his twenty-fifth year or thereabouts, requires 3200 calories. As he gets older, it drops off to 2400, and for the female it runs from 1800 to 2300 calories. Among children, the adolescent boy, 16 to 20 years of age, requires 3800 calories a day, just to maintain his activities and growth without any of the extra work involved if he is doing extracurricular work. Obviously, one cannot expect a diabetic patient to stay in good nutrition and be able to carry on his daily work and activities, when kept on starvation diets.

We promise a great deal to the diabetic. The American Diabetic Association issues literature entitled, "A diabetic can lead a full life." Then his physician prescribes a starvation diet. The symptomatology of many of these diabetics is comparable to that of people with malnutrition. They are tired, have lost their energy and they cannot do sustained work. It is largely because of the fact that diets are not adequate in calories, nor in protein, nor in the micronutrients which are required to maintain good nutrition essential for good health and longevity. My plea is to review the criteria for the diagnosis, classification of severity, and, above all, to review our therapeutic procedures and put them on a good normal nutritional basis.

In doing serum phosphate determinations simultaneously on these patients it is found that the serum phosphate levels will

decrease in some of them at the same rate as in people who have normal glucose tolerance. I do not believe that these people, even though they have an elevation of blood sugar at the end of two hours, are true diabetics, provided the phosphate level will go down and if, at the end of the third hour, their blood sugar level returns to approximately the fasting level.

DR. J. R. BEARD — Do you attach any significance to the height of the blood sugar at the end of the first hour? In other words, how do you interpret readings of 200 mg. or 190 mg., or under 175 mg.?

DR. POLLACK — No, I do not think the absolute height is of any major significance from the point of view of prognosis or indication of severity. But, again, I always like to know the method used in determining the blood sugar before making any guess as to what the blood sugar level means.

As pointed out before, if it is capillary blood analyzed by one of the old Folin tests, there can be, in nondiabetic persons, blood sugar levels up to 240 mg. and, if it were done by a Schaeffer method (a true blood sugar method) that would be of very serious significance.

DR. GEORGE GOODKIN — Were those figures you gave us, on the Folin Wu test, the results on specimens taken one hour after eating?

DR. POLLACK — Those were taken at one hour and thirty minutes after a meal containing 65 grams of carbohydrate. It was a mixed meal.

DR. GOODKIN — Dr. Pollack, can you tell us what percentage of juvenile diabetics attain the age of approximately 30 years at the present time?

DR. POLLACK — I reviewed those figures recently, and it depends on how old the child is when he developed his diabetes. That is one of the major criteria.

Children who develop diabetes after the age of 14 or 15 will reach their thirtieth year at the same rate as the nondiabetic children, without any question. The infants who develop diabetes in the first year of life have a much more difficult problem. The statistics on that are, of course, grossly inaccurate because

of the scarcity of the number of patients and the reporting. But we do have, in our own group, several patients who have had diabetes since the second year of life, and who are surviving into their thirties. That is about as close as I can get to it.

DR. JAMES H. HUMPHRIES — Would you like to discuss the two-hour test for glucose tolerance in the diagnosis of diabetes, particularly as it might pertain to our guidance in life insurance selection?

DR. POLLACK — By the two-hour test, you mean the single dose of glucose and the blood sugar determinations at fasting and a half hour, one hour or two hours, I suppose. I do not believe that that is as reliable a criterion as a three-hour test, because there will be a certain number of patients who will have elevated blood sugar at the end of the second hour, but who will not have an elevated blood sugar at the end of the third hour.

DR. R. K. FARNHAM — Would you comment on the blood sugar curves in obese subjects or those having marked overweight?

DR. POLLACK — Neuberger and Conn in 1934 published part of the story about the reversibility of the glucose tolerance curve in the obese patient. They studied a group of obese women who had diabetic types of glucose tolerance curves, according to all the criteria. With the therapeutic use of a weight reduction regime and loss in weight, practically all these patients experienced a reversion to a normal glucose tolerance type of curve. They pointed out that this, probably, was a liver phenomenon rather than a pancreatic insulin phenomenon.

I am always somewhat skeptical about these obese people. One does not see the reversibility of impaired glucose tolerance as a temporary phenomenon. We have followed some of these people over a long period of time, and a certain number of them will eventually become diabetic in accordance with our conventional standards of a then irreversible diabetic type of glucose tolerance curve.

I think that one must be extremely careful in saying that a person is not a diabetic, because the glucose tolerance curve has reverted to a normal type after there has been more than 10 per cent loss in body weight.

DR. RICHARD L. WILLIS — Dr. Pollack, I would like to ask you a question. In a group of persons with a blood sugar of 130 mg. or 140 mg. at two hours and returning to below 120 mg. in three hours, would you expect more cases of diabetes to develop than in a group in which it returns to 120 mg. or below in the shorter time of two hours?

DR. POLLACK — That would depend on the age group, Dr. Willis. I think that the criterion for normal blood sugar concentration is relative to age. If we were dealing with a population group over 50 years of age, and, at the end of the second hour the blood sugar level was 130 mg. and in the third hour it returned to 120 mg., I would pay less attention to the 130 mg. level at two hours than if it occurred in a younger age group. If the people were under 50 years of age and demonstrated that phenomenon, I would be suspicious and would want the test repeated. However, over the age of 50, there is less chance of its representing true impairment of glucose tolerance.

PRESIDENT WILLIS — Thank you, Dr. Pollack, for your splendid paper. We are so glad to learn from you more about the prognosis in diabetes mellitus.

Many of you will recall the discussion on arteriosclerosis before this group in 1950. Since that time, there have been changes in the concepts of this disease. It will be a pleasure to hear Dr. William Dock again. Dr. Dock is Professor of Medicine, State University of New York College of Medicine at New York City, and his subject is, "Present Concepts of Arteriosclerosis."

PRESENT CONCEPTS OF ARTERIOSCLEROSIS

WILLIAM DOCK, M. D.
Professor of Medicine
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Perhaps the title of this presentation should be "my present concepts", because in 1950, when I talked to you, I was one of a very small minority of doctors who thought that the composition of the diet was the most important factor in the pathogenesis of the atherosclerotic type of arteriosclerosis. There are still a number of very careful and experienced students of arteriosclerosis who think that diet either has no part at all in human arteriosclerosis or, if any, it is in a nonspecific way. They feel that obesity in some way causes arteriosclerosis, but the components of the diet which lead to obesity make no difference at all.

There were two panels last year on arteriosclerosis, one at the New York Academy of Medicine and one at the American College of Physicians. On each panel, there was one man who was an expert in the experimental production of arteriosclerosis in animals. Both men had found it quite impossible to produce anything that looks like human atherosclerosis without supplementing the animals' diets with cholesterol. Yet, the panels agreed in toto (except for me)—including these men who were producing experimental arteriosclerosis by feeding cholesterol—that cholesterol in the diet was of absolutely no importance whatever in human arteriosclerosis.

It is an extraordinary state of affairs. It is as though, in 1890, one got together a group to discuss the pathogenesis of tuberculosis, including people who had spent ten years studying tuberculosis produced in guinea pigs, and the panel members all agreed that the tubercle bacillus, important in the guinea pig, was of no importance in tuberculosis in man. That, literally, was the state of affairs which confronted me on these two panels. The audiences seemed quite pleased to know that diet was probably of no importance in the production of atherosclerosis. However, I will

give you concepts which have been shared by others more and more in the last year. My advantage is that I do not do any work in this field, I only read the literature.

In all the discussions of arteriosclerosis and diseases due to arteriosclerosis, such as angina pectoris, up to 1908, the writer always emphasized the fact that this was a disease of the rich and was not seen in the poor. Even in 1920, the last edition of Osler stated that arteriosclerosis and angina were not diseases of the poor but occurred, as Osler said, in "businessmen who eat, drink and smoke to excess". That was a simple clinical experience, and it is true today.

On ward rounds in the city hospitals of Madrid, Lima or Mexico City, one does not see any coronary disease at all, nor any diabetic patients with arteriosclerosis. Those with diabetes are seen dying of infections. However, patients seen there in consultation are invariably lawyers, doctors, politicians, and businessmen with coronary disease. Some of them will have had their first attack before the age of forty — a striking contrast in disease in two populations in the same city. This confirms what Osler and others said before 1920.

In the Russian empire, which was quite large even before the recent additions, the pathologists, who were extremely good, had noticed striking regional differences in the incidence and age at at death of atherosclerosis among the population in their country. This convinced these men that diet was the really important factor in causing arteriosclerosis.

In 1908, a Russian pathologist had two groups of rabbits, one on ordinary rabbit food and the other on a diet largely supplemented with meat and cheese. He noted that the rabbits on the latter diet got atherosclerosis and the others did not. This was confirmed in Germany within two years, and it was further shown that the protein fraction of these animal foods would not produce arteriosclerosis in the rabbit. It was in the fatty fraction.

It was then known that cholesterol was an important element in the lesions seen in the vessels of man and of these animals. In 1914, a Russian pathologist was able to report that by simply adding cholesterol to rabbit diets he could produce severe atherosclerosis. This, again, was confirmed in Germany and, in this

country, was studied extensively by Timothy Leary of Boston, who was led to the same conclusion as that of the Russians by the difference in incidence of atherosclerosis in different parts of the Boston population. The animal experiments, then, confirmed what clinical studies suggested.

The most ingenious one, perhaps, was a Japanese experiment, reported in 1922. A gentleman fed chickens their own eggs, and the chickens got atherosclerosis with great rapidity. Hens get a little atherosclerosis of the aorta even on a cholesterol-free diet, but the disease in the experimental hens, the ones eating their own eggs, was very much more rapid and appeared earlier in life. As you know, Drs. Stamler and Katz have an extensive experiment under way, in which chicks are given atherosclerosis of their arteries, including the coronary arteries, by supplementing their diets with cholesterol.

Dr. Wakerlin and Dr. Kendall have produced the disease in dogs, always using cholesterol as the essential feature of the experimental as contrasted with the control animals. At Harvard they have produced the disease in monkeys, always requiring one difference in the experimental group — cholesterol added to the diet.

It is a little hard to think that all this has no significance for man, since all the populations that get atherosclerosis do have a fair amount of cholesterol in the diet. The argument against this, which is considered very weighty by those who oppose the notion, is that man synthesizes cholesterol in his own tissues and in considerable quantity. Well, of course, rabbits synthesize cholesterol and very much faster per kilo per day than man does. The chicks synthesize cholesterol and they put it in their eggs and excrete it in their eggs in large quantities, year in and year out, on a cholesterol-free diet.

All this, of course, was known to Anitschow and to Leary. Everybody has known for a long, long time that cows had no cholesterol in their diet but a lot of cholesterol in milk, and that a calf's brain has 2.5 per cent cholesterol which must have been synthesized somewhere between the grass and the calf, because there is no cholesterol at all in the diet. To say that we recently

found out that animals synthesize cholesterol is nonsense. Everybody has known this since they began to study the problem.

What we can say now, therefore, is that cholesterol in the diet acts differently from cholesterol synthesized in the body. The most striking evidence of this is actually found in the rabbit. If soap-like substances are injected into the veins of rabbits, as mentioned in 1950 when we talked here, you can get rabbits to synthesize cholesterol very much more rapidly than they do normally, and they maintain blood levels of plasma cholesterol of 2000 mg. per cent or better. The normal level in the rabbit is 60. No matter how long these rabbits remain in a hypercholesteremic state they never show any atherosclerosis. This work was done by Kellner at the New York Hospital and has been confirmed in other places.

The most extraordinary situation in relation to human diabetes, and the thing that makes one wonder whether animal and man are in any way related, is that rabbits made diabetic by treatment with alloxan also have high blood cholesterols, on a cholesterol-free diet, but these rabbits also show no atherosclerosis with levels of 2000 mg. per cent, whereas, at 200 mg. per cent, due to feeding cholesterol to rabbits, one gets rapidly progressive disease. We are quite sure now that endogenous cholesterol is of very little significance, except in one respect.

We all release cholesterol into our gut, and, if we are on a cholesterol-free diet, this is endogenous cholesterol which goes into the bile, helps digestion and helps to absorb and transport fat. The amount of cholesterol that goes into the gut depends to some extent on the fat in the diet. On a fat-free diet, biliary stasis occurs. The gallbladder does not contract after meals. The liver does not have as rapid a recirculation of bile acids and cholesterol, and the total amount of cholesterol entering the gut per day, on a fat-free diet, is considerably less than on a diet that contains fat. Therefore, if you put people on a fat-free diet, their endogenous reabsorption of cholesterol certainly drops, and, in so far as we can tell, the effect of biliary cholesterol and of dietary cholesterol is probably much the same in relation to atherosclerosis.

Once this cholesterol enters the body from the gut, it is dis-

posed of in a fairly rapid fashion. Some of it is just degraded or excreted, some of it is incorporated into the cholesterol that is produced by the liver, which always seems to enter the blood stream as relatively soluble cholesterol-protein molecules. These do not contribute to atherosclerosis. Along with these soluble molecules, there is some cholesterol which has been more recently absorbed and is in a more insoluble form. In many men, this relatively insoluble form precipitates out in the linings of the coronary arteries more rapidly than it does in the aorta. In men and women, aortic atherosclerosis proceeds at about the same rate, but coronary atherosclerosis is much more rapid in men than in women, and more rapid in male chicks than in female chicks. After women pass the menopause, their coronaries lose this relative immunity, and their coronary atherosclerosis proceeds at about the same rate as it does in men of the same age.

Drs. Katz and Stamler have shown that in chicks, giving estrogens produces a change in the cholesterol pattern, which slows down coronary but not aortic disease, in male chicks that have high estrogen levels.

Coronary arteries have a different kind of intimal structure from the aorta and the other vessels in the body. They have cushions of very loose tissue, in which there is longitudinal smooth muscle. This has been known for a very long time and is in the best handbooks of histology, but, apparently, it is not in the pathology textbooks. In a recent article on the war dead in Korea, it is stated that the Americans had a great deal of lipid infiltration of the coronary arteries, and that the Koreans had fat-free coronary lesions. These coronary lesions in the Koreans are normal structures, seen in newborn infants, in newborn dogs, in newborn or new-hatched chicks, and they have been described for a long time and discussed in great detail in von Möllendorf, the classical encyclopedia of histology. Every pathologist should read this before he begins to look at diseased tissue. It is a good thing to know what the normal looks like before beginning to write about disease.

At any rate, coronary arteries behave differently from the aorta, they are different structurally, and, curiously enough, the difference in lipid patterns in men and women at the age of sexual activity is such that the material precipitates out in the aorta at the

same rate but at different rates in the coronary intima. This is something about which we are now quite sure. We also know that by giving men estrogens in doses that cause complete emasculinization, with loss of libido and potentia, the pattern of plasma lipids, of alpha and beta globulin-bound cholesterol, or of Gofman fractions, changes in young men to the same pattern as we normally see in young women. Therefore, one way to slow coronary disease and accelerate formation of gallstones is to change your endocrine pattern from male to female. It is easy, of course, to take out gallstones, easier than it is to repair a damaged coronary artery.

What is the situation about the diet at the moment, as regards men? I think it has now been completely cleared up. The mystery has not been cleared up, but the situation has, by work done by Ahrens and his group at the Rockefeller Institute. This work should have been done about thirty-five years ago, and it illustrates the way people like to make the wrong experiment rather than the right one. Dr. Ahrens took some obese people and kept them on diets on which they lost no weight during the entire experiment. Their diets were always rich in fat; nearly 40 per cent of their calories always came from fat. The difference was that at one feeding period, the fat was of animal origin and contained about a gram of cholesterol a day, and in the other feeding period, the diet had no animal fat, only vegetable fat, and no cholesterol. On the average, in the first six people that he studied, the blood cholesterol rose 30 per cent, when they were switched from vegetable fat diets to animal fat diets, with the same fat and the same caloric intake.

In a group of studies recently reported from Ontario, similar work was done. The feeding periods were of only eight days' duration. Yet, in eight days, on one regime or another, there were striking changes in the level of blood cholesterol in a large group of volunteer subjects, none of whom were particularly obese or particularly lean. This is a general phenomenon, therefore. On a vegetable fat diet, the cholesterol level in the plasma, and particularly the atherogenetic fraction of cholesterol, will be low. On an animal fat diet which contains different fatty acids and also contains cholesterol, it will be higher.

We now know that the protein content of the diet is very important, because, on low protein diets, certain species of dogs and monkeys develop high blood cholesterol levels, which, at a higher protein level in the diet, do not occur. This probably is also true of man, and therefore the protein content of our diet should be adequate, and the fat content should be derived largely from vegetables. This will automatically ensure our getting very little cholesterol. Dairy products are especially dangerous when, as in this country, producers throw away the protein. We give this to hogs or use it for glue. We put the fatty fraction in butter and ice cream, for which we have a great addiction. Some of us like sour cream and some of us like whipped cream, so that in this country, the intake of low protein, high fat material is perfectly fabulous. No other country has approached us in the way they take a high animal fat food, with low protein content. Eggs also have a relatively low ratio of protein to animal fat and cholesterol. We, more than any other people in the world, eat a diet which contains two foods which were never intended by nature for human consumption. Eggs were intended to produce little chickens, and milk was intended by nature to raise animals until their teeth allowed them to chew. That is what milk and eggs were intended for by nature, and, as Hippocrates and a few other doctors since have pointed out, whenever man does something which nature does not intend, he gets into trouble.

One of the things that nature did not intend, of course, was that we should be smoking nicotine-filled cigarettes all day. This did not begin until long after we had gotten on a relatively high protein, high cholesterol, high fat diet. Such a diet has been available since Roman times at least, but only for the rich. Smoking is a new factor.

Dr. Gofman finds that smoking actually raises the fraction of abnormal or undesirable protein-containing lipid in our plasma and that smokers on the same diets have higher levels of pathogenetic cholesterol in their plasma than have nonsmokers. I do not know whether this will be confirmed, or what the mechanism will be. Perhaps splanchnic vasoconstriction, which smoking produces, may well change the capacity of the liver to deal with ingested cholesterol.

We know that exercise alone improves the rate at which the body rids itself of absorbed cholesterol. An energetic fellow, as experiments at Harvard by Mann have shown, on a certain diet, has a certain level of blood cholesterol. If you leave his diet just the same and stop his exercise, his blood cholesterol and his weight both go up. His cholesterol does not necessarily rise because the weight goes up, but because his total metabolic turnover has been reduced.

Similarly, smoking, which causes vasoconstriction of visceral vessels, may change the function of the liver to some extent, and prolong the stay of undesirable cholesterol in the plasma. Another thing smoking does is to cause vasoconstriction in the arterioles in the heart. If the heart has had a little coronary trouble and is dependent on collaterals, it does not work as well when the collateral undergoes vasoconstriction. In any event, the age at death of a-pack-a-day cigarette smokers from coronary disease is about ten years less than the age at death of nonsmokers with coronary disease. They all die of coronary disease, but one group has to stay around and meet the bills for ten years longer. If a person had no excess of cholesterol entering his body from an abnormal diet, I do not believe that any amount of smoking would give him coronary disease, but with the combination, the death rate is now going up, and the age at death is steadily falling.

The British have had a gloomy experience. Their death rate from coronary disease was well below ours. In the British army, the death rate from coronary disease was probably, in men under 35, 10 per cent of that in the American army, during the period when the British were at war and we were in training. The reason for this is obviously in the diet. Both armies were smoking continuously, around the clock, so that cigarette consumption had nothing to do with it. It was merely a question of a low fat, low cholesterol content of the British diet, and a high level of dairy products and eggs in the diet of our Army and Navy.

At any rate, now, the British rate is going up. Instead of the British doctors dying six years older than American doctors, they will soon catch up with us. The reason is that they have learned how to produce eggs in these factories where the hen never moves all day long. The British Society for the Prevention of Cruelty

to Animals wants to do something about this, but egg production and consumption in England are rising rapidly. They now have cheap oleo-margarine. It comes from whales and it has nearly as much cholesterol as butter. It is quite different from our oleo-margarine, which comes from corn oil and cotton-seed oil. The British are trying their best to catch up with us in this respect, and to see if they cannot lower the age of incidence of coronary disease in their population.

This, at the moment then, seems to be the situation. We do not know why vegetable fat diets lower the cholesterol level of the plasma at any given intake of cholesterol. Nor do we know whether they contain blocking agents, or whether the fatty acids in the vegetable oil hasten the rate at which the body can dispose of absorbed cholesterol. We do know that if one wants to postpone the age at death from coronary disease, one will have as much vegetable fat — olive oil, cotton-seed oil, corn oil — as possible in the diet, and a low intake of dairy fat, egg fat, and animal fat in general.

Our own regime for our patients is to let them eat all the lean meat and all the lean fish they want, but to keep away from the fatty types of fish and meat, because it is not necessary to eat these. This is hard on the hog farmers and it is hard on the Kansas City fattening business, because all the weight they put on a cow in a feeding lot decreases the amount of protein and adds to the amount of fat. Steers off the range may not be as tender but they are much better for your body than ones which have been fattened up in the feeding yards.

Lean meat, plenty of cereals and vegetables of any kind, any kind of vegetable oil, and all the fruit you want would, presumably, be the proper diet. This, of course, was the diet which nearly all people over most of the world were living on until quite recently, and it is the diet of the poor everywhere. The price of the diet of the prosperous is early or late atherosclerosis.

The men who worked at the Pekin Medical School — Dr. Keefer and Dr. Snapper — were very much impressed by the absence of arteriosclerotic gangrene in middle-aged and elderly Chinese diabetics. One reason was that they were dying from infections,

quite a large number of them, but some of them lived to a good old age, and in our country, some of these certainly would have had trouble with their legs. They never saw a leg amputated in a diabetic in Pekin, in the sixteen years of experience after insulin was available to them. They saw no diabetic retinitis, and they saw no renal lesions, such as we see in our diabetics.

It seems almost certain that the curious type of atherosclerosis that diabetics have — and they have a high incidence of coronary disease as well — is related to the type of diet. The sort of diet I have mentioned is more important to a diabetic individual than to anyone else, because his prognosis now depends not on the severity of his diabetes, but on the way in which his body handles the cholesterol that he absorbs and on the amount of cholesterol which he gets every day and the sort of fat that comes in with it.

In closing, I should like to reinforce what Dr. Levine told you the other day, about the management of acute attacks, because a third of you will have attacks of coronary occlusion. We know how a distinguished son of Kansas is being taken care of by the best medical brains available for important people. Dr. Levine and I have managed our patients that way for a quarter of a century but for the last 5 to 10 years we managed them very differently. I changed my management in 1944 and Dr. Levine, Dr. Tinsley Harrison and I, on a lead that we got from the late Dr. Frank Wilson of Ann Arbor, have all given up the six weeks' bed rest (which Dr. Levine, incidentally, introduced) to another regime. In a recent article in the Journal of the American Medical Association, Dr. Edwin Wood, of Virginia, reported on the relative value of complete bed rest versus the so-called armchair treatment of acute myocardial infarction. His statistics show that when he studied comparable groups, managed in the two ways, the death rate was twice as high in those who were kept bedfast for weeks. This was true both in cases classified as moderately severe and those considered to be much milder. Whether it is a mild attack or a severe attack, perhaps involving shock at the onset, the longer the patient lies in bed, the greater the chance that he will never get out of it. I do not believe the difference in death rate will prove to be as great as in this report, but I do believe that the rate is lower when sitting is permitted. The first report from Sweden

on cases treated in the chair, as compared with controls kept in bed, was given by Helander. He, like Wood, found nearly twice as high a death rate in the group who were kept in bed.

The most striking thing is to talk to our patients who have been treated by one method in the first attack and by the other method in their second attack. All of them agree that they got along much better when they were managed by armchair treatment, and we know now that more of them are alive to tell the story. More of them survived and they agree that this treatment is better.

This is something for all to consider whenever you get your myocardial infarction. In the normal state of man, assuming that he would rather eat and enjoy life than go on some sort of undesirable feeding regime, there is one chance in three that he will have a myocardial infarction. We are quite sure that the armchair treatment is more humane, more physiological, and better from the economic standpoint. It offers a better chance of survival than the classical six weeks of bed rest, and after recovery, how to prevent a new episode seems to us much clearer than when we talked to you in 1950.

DR. F. J. MCGURL — I would like to ask if there is any method by which you can reverse the arteriosclerotic process when it has developed.

DR. DOCK — The studies that were done in Germany in World War I by Aschoff's group showed that atherosclerosis diminished in the German population during what was known as the *Hunger Zeit*. They did not get much protein, but they got almost no animal fat. This was the first evidence from human pathology that the disease was reversible.

In rabbits, it is easily reversible and it reverses normally. Dr. Bragdon at the National Institute of Health has shown that every baby rabbit, while suckling, has a blood cholesterol which is three times the level of adult or newborn rabbits. It is 200 mg. per cent instead of 60. All these suckling rabbits — their mothers' milk has three times as much cholesterol as human milk — get cholesterosis of the aorta, and if you keep on feeding them cholesterol at that rate this develops into ordinary progressive yellow lesions. When the baby rabbits are weaned, all of this deposition of choles-

terol and evidence of reaction to it disappear very quickly. Of course, rabbits metabolize things rapidly.

Dr. Wilens has shown that people who had a long wasting illness and ate very little because of their illness, had less fresh atherosclerosis. They might have a great deal of calcium in their arteries but florid, fresh lesions were much less than in the Bellevue patients dying suddenly from any cause. So the evidence is quite good that the acute lesion is to some extent reversible.

Therefore, we think that the actual lesions are reversible, but, from the standpoint of practicality, this is really not important. Collaterals develop very rapidly when a vessel is closed off. When it is closed off, if there is no collateral circulation, some tissue will die beyond it. This tissue dies in the heart and a scar takes its place. The collateral provides plenty of circulation for the muscle in the neighborhood, in most patients. If further atherosclerosis does not develop, this collateral will prevent further trouble for an indefinite period of time. In other words, the ordinary thing is a race between atherosclerosis in the coronaries and the collateral formation. If we reduce the rate of atheroma formation, so that the collateral will stay well ahead in this race, the prognosis is very much better.

DR. KARL W. ANDERSON — Dr. Dock, have you followed any groups of vegetarians in this country?

DR. DOCK — The group at Harvard has studied some vegetarians in California. They examined young vegetarians of the pure variety, and vegetarians who are known as "ovolacto-vegetarians", who use eggs and milk but do not actually kill any animals. The ovolacto-vegetarians had blood cholesterol levels only three per cent below those of controls. The pure vegetarians had blood cholesterols 30 per cent below those of controls.

These California vegetarians eat a lot of nuts. They have a high protein and a high fat intake because of the diet of nuts and the use of salad dressing which has vegetable oil in it. The longer survival of these people has been known for decades. While vegetarians last longer than nonvegetarians, some people think this is because they are odd characters, and are not as exposed to the ordinary hazards of life as other people. At any rate, vegetarians do live longer than ordinary people.

DR. D. J. BREITHAUPT — You mentioned the people who have a little calcium in their arteries. I was wondering if you would try to give us some clue as to what you think the significance of this is. We occasionally get applicants for insurance who have a calcific plaque in the arch of the aorta or, perhaps, a deposit in their pelvic veins or leg veins, as their doctor tells us. Is this important, and is it more important in a 40 year old than a 60 year old person?

DR. DOCK — In part, I think, the deposition of chalk is due to the fact that with our high dairy product intake, we have plenty of available calcium. It is a striking feature of arteriosclerosis in our part of the world that the lesions, after a certain period of time, have chalk in them. The chalk in the ascending aorta has an extremely ominous prognostic significance. It almost always means that the patient has syphilitic aortitis. This is when you see it between the root of the aorta and the place where the aorta crosses the midline, as it goes from right to left, in the upper part of the chest.

This has been well known for a long time, and here, again, the interesting thing is that in China, they not only have practically no cholesterol gallstones, but you can not tell whether a patient has aortitis by finding chalk, because the Chinese with aortitis have no superimposed atherosclerosis, and calcification. The chalk in the knob to the left of the midline means that the patient has atherosclerosis, but he has atherosclerosis on the arch of the aorta, where it seems to be relatively unimportant prognostically. It is not quite unimportant, because people who have this also have more chalk in the abdominal aorta, and people who have more chalk in the abdominal aorta and in the iliac arteries do risk vascular disasters at advanced age. Albert Einstein was one of the people who died, not from his coronary atherosclerosis but from his abdominal atherosclerosis. If there is no chalk at all, there is no chance of one's getting this rather rare disease. If there is chalk in the arch of the aorta, there is probably some in the abdominal aorta and, with this, ulcerative lesions. If one lives long enough, these may become the cause of illness and death. Therefore, it has some prognostic significance, but it does not give any clue at all as to what is going on in the coronary arteries.

Women have these lesions just as often as men, at ages when coronary disease in women is much less frequent than in men.

DR. HARRY E. UNGERLEIDER — How do you explain the fact that mortality rates among farmers are the lowest in the United States? They practically live on a high fat, dairy diet. The next group, of course, is the professional and business people, and, if we go down the socio-economic scale, the mortality rate increases. But the farmers in the United States seem to have the best mortality rate, and they seem to live on this high animal fat diet.

DR. DOCK — I am not sure that the figures for farmers are correct, because this includes sharecroppers who are on a very low income and a very poor diet. It includes all the cattlemen who never touch milk if they can help it, and it includes a large number of farmers who have modest incomes and to whom the fat in what they produce is their chief cash crop — they sell it and they eat protein.

Among prosperous farmers in Minnesota, Iowa, and Kansas, I gather from my doctor friends, there is a very good incidence of early coronary disease, just as in businessmen. Once a farmer takes to a tractor instead of sweating with his own muscles, and has the same diet as a businessman, the fact that he is riding a tractor instead of an automobile gives him no immunity to coronary disease. I do not think there is any evidence at all that men who have a home in the country but have the same diets and the same amount of daily energy liberation as do businessmen and doctors, have any immunity to coronary disease. A lot of us around here live in the country and commute to town, and our coronary disease is just the same as that of everybody else.

The work reported by Mann showed that a man who did physical labor, a lumberjack or a farmer of the old school, who got up at four o'clock and worked with his own muscles for many hours every day, was more likely to have a later onset of coronary disease than a person who was leading a relatively sedentary life. But the farmers are becoming more and more sedentary, except the laborers whom they hire, usually in the Southwest, who are Mexicans living on a very low cholesterol diet. There is not much cholesterol in cornmeal and beans, which is the

principal diet of many people who are now doing the work on the farms. This gives us figures indicating that the poor man on a farm has a low coronary death rate, prosperous men who own farms die of coronary disease at the same rate as those who own any other kind of business.

The question of work was first brought to light by the statistics from London, which showed that the conductors of buses in England have a later onset of coronary disease, and, at any age, therefore, a lower incidence of coronary disease than the bus drivers. This was ascribed to stress, for the bus driver was fighting the British traffic and the conductor was just fighting the passengers. But it seems now that the situation is not quite so simple.

The British buses are all doubledeckers, and the conductor on a British bus climbs about two thousand feet a day, collecting his fares, whereas the bus driver does not climb at all. This may fit into Mann's observation that, for any given dietary intake, the person who spends a lot of energy in physical work will have a lower blood cholesterol and, presumably, a later onset of coronary disease than the person who is in a sedentary occupation.

DR. R. K. FARNHAM — Dr. Dock, would you comment on the advisability of taking thyroid extract for the purpose of keeping the serum cholesterol down in some of these cases?

DR. DOCK — If it can be demonstrated, in any given person, that thyroid extract, without upsetting him in any way, or perhaps even making him feel better, lowers his blood cholesterol — maintaining a constant dietary background — I would say that he should continue to take thyroid extract all his life.

The ordinary feeling now is that a normal person with a normal thyroid can eat at least five grains of thyroid extract a day without having any real effect, either on the metabolism or the cholesterol level. The normal thyroid not only makes thyroxin but it can also turn off its own production and actually destroy excess thyroxin that gets into the body from any source. The iodine uptake of the thyroid simply stops in a patient who is eating thyroid extract. Presumably a fall in cholesterol occurs only in a patient whose thyroid was to some extent less active in producing and destroying thyroid than the normal.

Some people, including Dr. James B. Means, believe that thyroid insufficiency is an all-or-none business. One either has good thyroid activity or practically no thyroid function. When there is no thyroid function, a small dose of thyroid extract, half a grain a day, makes quite a difference in the cholesterol level and in heat production. But, with a normal individual five grains of thyroid extract a day may have no effect whatever on the cholesterol level, the oxygen consumption or indeed on anything else. The patient does not feel badly. If the thyroid dosage is increased to the point where a rise in the basal pulse rate occurs, the cholesterol level always begins to decrease. Be sure to have the patient on thyroid medication record the pulse rate every morning, in bed and before he becomes active. If this does not change, the thyroid extract really is not affecting him much, unless he has complete heart block. If it increases 10 or 15 per cent, he is getting a metabolic effect of thyroid and almost certainly his cholesterol will be lower. That is the easiest way to control thyroid dosage when enthusiastic about thyroid therapy for middleaged people who have no specific signs of hypothyroidism.

PRESIDENT WILLIS — Thank you, Dr. Dock, for that wonderful talk on a subject that is most important to us. The applause is evidence of the appreciation of your audience. We enjoyed you even more than we did five years ago.

All of us have studied the recent Impairment Study of the Society of Actuaries, but few of us have had the opportunity of hearing an actuarial expert on risk selection discuss this subject. Mr. Webster, like many actuaries, is a native of Scotland, but, for many years, has been well known and highly regarded in the insurance industry in this country. He is a Fellow of the Society of Actuaries, and Vice-President for Selection of The Mutual Life Insurance Company of New York. It is a pleasure to introduce Mr. Andrew Cameron Webster.

COMMENTS ON THE 1951 IMPAIRMENT STUDY

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In view of the many discussions of the Study that have appeared since its publication another discussion may seem superflous. There are, it is suggested, three aspects to the Study. The members of this Association have more than ordinary interest in the clinical aspect in so far as the Study extends our knowledge of the effect of certain impairments on longevity. The actuaries are interested in the statistical side, and not only because of the statistical problems but also because of the long range effects upon the companies they represent as far as extra premiums, more accurate pricing, and mortality gains are concerned. The third aspect might be described as the point of view of the practical underwriter, the individual who, be he doctor or layman, is faced with the material contained in the Study and has to translate this into appropriate ratings, if such are called for.

This is not as easy as it looks, and while this discussion may not make it any easier it will describe as simply as possible one way of approaching the problem.

Before discussing any illustrative impairments the following several points should be mentioned.

1) The statistical limitations of the Study: The results are subject to statistical limitations, well measured by the *probable error* and the *confidence interval.* Both these measures are explained in the text, and there is a discussion of the probable error by John R. Larus in your own PROCEEDINGS, Vol. XXIII. All the figures should be read with these qualifications in mind, and an underwriter might well prefer the pessimistic to the optimistic approach. An improving mortality has made optimists of us all, but extra deaths are still extra deaths and have to be compensated for.

2) Then there are the limitations of the Study itself. The experience is triangular in shape, as shown in table 1.

TABLE 1

Year of Exposure Ending In*

Year of Issue	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946
1935	1	2	3	4	5	6	7	8	9	10	11
1936		1	2	3	4	5	6	7	8	9	10
1937			1	2	3	4	5	6	7	8	9
1938				1	2	3	4	5	6	7	8
1939					1	2	3	4	5	6	7
1940						1	2	3	4	5	6
1941							1	2	3	4	5
1942								1	2	3	4
1943									1	2	3
1944										1	2
1945											1

*This table is not complete — it is merely illustrative.

The exposure covers 15 first policy years, 14 second policy years, and so on, to only one 15th policy year. Now the total first year experience covers various underwriting patterns. No underwriting department has a record of 15 years continuance of the same underwriting standards, either for standard or substandard business. No underwriting department should have, for that matter.

3) The experience is heterogeneous in another respect. Not only are there variations in the underwriting patterns of the individual company, but also, in some impairments at least, there are different interpretations and classifications of the impairment. The text contains warnings also as to the effect of an over-large contribution by any one company to the experience on any one impairment.

4) In interpreting the Study we should bear in mind the practical pattern of substandard practice throughout the industry. Extra premiums for extra mortality take one of two forms. Either the extra premium is calculated on a mortality table

showing certain percentages of the standard rate of mortality, 150 per cent, 200 per cent, 250 per cent, or a flat extra premium is charged for a limited number of years. There are exceptions to both of these types of extra premium but, by and large, they are the practice of most companies. The first method, the percentage extra, assumes a hazard increasing with age, and the second, the flat extra, assumes a hazard decreasing with duration but constant with age. A brief review of any mortality study will show that the incidence of extra mortality does not always follow either of these patterns. These methods, however, have practical advantages, and it is obviously impossible to tailor the extra premiums to the varying types of substandard mortality, even if we were sure of the mortality trends. It is logical, therefore, to look at the results to see if they can be fitted into either of these patterns, bearing in mind that the extra premium is not going to fit the experience at all points.

This problem of increasing and decreasing mortality is an interesting one. An analysis of the various impairments studied shows that the commonest pattern of the extra mortality found appears to be approximately a constant percentage, or a slightly decreasing percentage of the standard by duration. The Canadian Association of Actuaries in connection with a recent discussion of substandard mortality gave the experience by duration of all classifications in the Study where the total mortality exceeded 125 per cent, and this showed:

Duration	*Actual/Expected*
1 - 5 yrs.	179%
6 - 10	167
11 - 15	151

showing an extra mortality decreasing with increasing duration.

The problem of finding appropriate ratings can perhaps best be shown by analyzing the results of some of the individual impairments to be considered. The first is the impairment with one of the largest exposures in the Study. Table 2 shows the mortality ratios and the extra deaths per thousand.

TABLE 2

A 7 — Apex murmur, systolic constant, transmitted to the left, and/or mitral regurgitation, without hypertrophy, found on examination, not known to have had x-ray or fluoroscope for diagnosis

Ages at issue	Mortality ratio	Extra deaths per M	Duration	Mortality ratio	Extra deaths per M
15 - 29	325	2.5	1 - 2	237	2.1
30 - 39	227	2.8	3 - 5	251	3.7
40 - 49	210	5.7	6 - 10	196	3.3
50 - 64	152	5.6	11 - 15	211	6.0
15 - 64	220	3.4	1 - 15	220	3.4

The mortality ratio does not form a pattern constant by age at issue though it is approximately constant by duration. The extra deaths per thousand vary both by age at issue and by duration, showing that a flat extra premium at all ages is of little value. There is a definite break in this table at ages below and above 40, suggesting that a flat extra varying by age might be satisfactory. Notice, however, that the flat extra at the younger ages may be inadequate by duration.

Investigation of the usual ratings for this impairment will show that the numerical debit for the impairment is probably plus 100. This does not conform to the range of mortality ratios revealed in the study, the debit being inadequate at ages under 30 but, on the other hand, more than adequate at ages over 49. By duration the debit is adequate. Therefore, the findings could well be translated into a debit varying by age at issue. Such a practice could be tested against the results of the individual age groups where the results are statistically significant. Table 3, compiled from the basic material, shows the results by age-at-issue groups and duration within these groups.

TABLE 3

A 7 — Apex murmur, systolic constant, transmitted to the left, and/or mitral regurgitation, without hypertrophy, found on examination, not known to have had x-ray or fluoroscope for diagnosis

A 7 — Mortality Ratio

Duration	Ages 15 - 29	Ages 30 - 39	Ages 40 - 49	Ages 50 - 64
1 - 2	282 (35)	295 (33)	238 (37)	141 (18)
3 - 5	377 (65)	264 (52)	246 (75)	159 (39)
6 - 10	326 (65)	185 (57)	177 (84)	149 (45)
11 - 15	277 (23)	219 (36)	209 (52)	157 (18)
1 - 15	325 (188)	227 (178)	210 (248)	152 (120)

(Figures in parenthesis show number of deaths)

The practice of varying the debit by age at issue may result in problems concerning reduction in rating as the insured life gets older. If the insured qualifies for new insurance at a lower rate it may be necessary to reduce the old rating, and the experience may not justify this since there is no consistent pattern of a decreasing percentage mortality by duration. It may be assumed, on the other hand, that in the experience such reductions have been made effective and that the results of the Study represent the true experience of the survivors.

One striking fact about the results on A 7 is the much lower percentage mortality in the upper age groups. This may not mean that applicants with this murmur at issue ages 50 - 64 are better risks than at ages under 50. It may be the result of stricter selection. The criteria for acceptance at the upper ages may be more severe. If, therefore, it is proposed to use a lower debit at ages 50 - 64 it is also necessary to continue the same strict underwriting if the debit is going to be adequate.

The real test of the adequacy of the ratings for any impairment is whether the extra premiums received are adequate to meet the extra mortality, sufficient to pay the extra death claims. This is more of an actuarial than an underwriting question because all substandard extras are gross premiums having to provide for expenses. They are also, in effect, relative to the scale of standard

premiums in that the standard premiums are not based, for example, on the Basic Table which was used as the measure in the Impairment Study. For a rough test a special scale of extra premiums allowing for a 200 per cent mortality for the period covered by the exposure was constructed and tested against the published experience, as shown in table 4.

TABLE 4

A 7 — Apex murmur, systolic constant, transmitted to the left, and/or mitral regurgitation, without hypertrophy, found on examination, not known to have had x-ray or fluoroscope for diagnosis

Central Age	Extra premium per M	Exposure	Extra premium x exposure	Extra deaths
22	3.50	56,602	198	130
34	5.00	35,784	179	100
44	7.50	23,002	172	130
57	14.00	7,328	103	41
			652	401

The extra premiums are an approximation of what would be charged, bearing in mind the limitations mentioned. It would be a mistake to conclude from this table that the substandard extras are excessive; the only conclusion derivable from the table is that they are adequate even at the younger issue ages where (see table 2) the Actual to Expected ratio was in excess of 200 per cent. A true test of adequacy requires a more elaborate investigation. The actuary can help with this and can also assist in making a rough check of the adequacy of the extra premiums.

There is another important point in making mortality comparisons between the results of a particular company and the results of a joint study either on a standard or a substandard basis. Before making a check of the experience under an impairment it might be desirable to be sure that the standard mortality of the company, either by accident or design, does not differ greatly on the higher side from the Basic Table used as a comparison in the Study. Several companies, as a matter of policy, sometimes as a matter of geographical location, underwrite a standard mortality nearer 125 per cent than 100 per cent of normal.

Such a company might, therefore, properly adjust the mortality ratios by increasing the expected deaths 25 per cent. If this is done under A 7 the mortality ratio reduces to 176 per cent. Time and space do not permit enlarging on the problem; it is one for the actuary and the executive officers, but it is still one of dollars and cents.

Considering the heart murmurs further, it is interesting to review *A-9, Apex murmur, systolic, constant, transmitted to the left, and/or mitral regurgitation, with moderate hypertrophy, found on examination, not known to have had x-ray or fluoroscope for diagnosis* because of the wide range in the mortality ratios. At ages 15 - 29 the ratio is 1311 per cent; at ages 30 - 39 1190 per cent; and the overall ratio is 601 per cent. These are well beyond any percentage ratings that would be considered under the usual extra premium percentage tables. To consider insuring this group one might consider the mortality in terms of extra deaths per thousand, (ignoring for the minute the warnings about probable errors and confidence intervals) to see if the extra mortality can be met by this method. Table 5 shows the figures.

TABLE 5

A 9 — Apex murmur, systolic, constant, transmitted to the left, and/or mitral regurgitation, with moderate hypertrophy, found on examination, not known to have had x-ray or fluoroscope for diagnosis

Ages at issue	Mortality ratio	Extra deaths per M	Duration	Mortality ratio	Extra deaths per M
15 - 29	1311%	12	1 - 2	1096%	15
30 - 39	1190	22	3 - 5	325	6
40 - 49	189	4	6 - 10	615	19
50 - 64	227	13	11 - 15	526	30
All	601	14	All	601	14

This is a slightly unusual result A *net* extra of $14 per thousand would cover the hazard if the company experience paralleled that of the Study, but it might be inadequate if there were more survivors in the 11 - 15 durations and more than adequate if all the experience was between ages 40 - 49. The net extra at ages under 40 is $17 per thousand, suggesting that the hazard might

be met in these cases by a flat charge per thousand. The group, however, is too small to permit drawing any conclusions therefrom — it is included to illustrate a method of approach to underwriting a group where the percentage method is obviously impractical.

The next group is one that has been concerning all underwriters because of the poor experience — peptic ulcer. The Study properly devotes a considerable space to peptic ulcer; twenty-six classes in all were investigated and results are given for twelve of these, some of them in combination. Underwriting practice has varied greatly between companies, particularly following the 1936 Impairment Study. There may be more than normal lack of homogeneity in the data because of this, and perhaps the only reliable statistics from a classification point of view are those relating to policyholders who had operations for ulcer. Incidentally, this is one impairment where the problem of lower female mortality which is discussed in the text of the Study does not affect the ratios since most of the entrants were males.

In both gastric and duodenal ulcers *without operation* there is some evidence that mortality decreases with duration and becomes standard, indicating that a temporary extra will cover the hazard. The *gastric ulcer without operation* groups provide a good example of the problems of translation. There are some strange statistics, for example, in D 7 *"Gastric ulcer, one attack, within 3 - 5 years of application, not known to have had hemorrhage"* the overall mortality is standard (116 per cent) and apart from the first two years (198 per cent) is within normal limits by duration. Yet the mortality ratio from digestive diseases is 521 per cent — suggesting that the first two years' deaths were all from digestive diseases. In the next group, D 8, where the attack was within 6-10 years of application the mortality ratio is below 100 per cent at all ages and durations, and yet the mortality ratio is 294 per cent from digestive diseases.

Some experience of underwriting ulcers suggests that many of the cases entering into the experience were underwritten on

limited information and that, therefore, the whole set of studies D 6 - D 10 covering *"Gastric ulcer without operaion, hemorrhage not known"* might be combined to see what the result is.

TABLE 6

D 6 - D 10 — Gastric ulcer without operation, hemorrhage not known

Ages at issue	Mortality ratio	Extra deaths per M	Duration	Mortality ratio	Extra deaths per M
15 - 29	200.84	1.2	1 - 2	156.58	1.07
30 - 39	107.63	.16	3 - 5	100.00	—
40 - 49	122.29	1.1	6 - 10	104.58	.33
50 - 64	75.25	—	11 - 15	100.00	—
	109.82			109.82	.35

It would seem from the duration table that the hazard is restricted to the first two policy years. A financial test such as outlined previously is a simple one, and the more or less usual practice of charging a flat extra for one or two years would seem to provide adequate coverage. There are, however, other considerations. Medically, it is believed that gastric ulcers tend to recur, and on that assumption some deferred extra mortality might be expected. Theoretically at least, the temporary extra should provide for this. The figures in table 6 do not bear out the suggestion of a deferred mortality — see the result at durations 11 - 15. There is some question of how valid the basic statistics may be. The class is an indefinite one, and in the absence of many of the current aids to diagnosis is it possible that it has been diluted with many risks who had not true ulcer histories? Nowadays the diagnosis is more likely to be accurate and perhaps the future experience being a truer sample will not follow the ratings suggested by the current statistics.

In the group with operations under D 13, *"Gastric ulcer with operation, one attack, within 6 - 10 years of application"*, the standard experience (231 per cent) is worse than the substandard (147 per cent), indicating some loose (or liberal) underwriting. Possibly the combined statistics will give a better picture of the hazard and table 7 shows the figures.

TABLE 7

D 13 — Standard and Substandard

Age at issue	Actual deaths	Mortality ratio	Extra deaths per M	Duration	Actual deaths	Mortality ratio	Extra deaths per M
15 - 29	2	104	0	1 - 2	19	238	3.0
30 - 39	22	171	1.6	3 - 5	22	138	1.4
40 - 49	51	221	6.4	6 - 10	48	197	5.6
50 - 64	36	162	7.3	11 - 15	22	184	7.5
	111	184	3.8		111	184	3.8

Outside of the 15 - 29 age group (where there are only two deaths) the mortality ratios are not too widely apart. The picture by duration is less clear, although it suggests a constant percentage mortality by duration. A percentage extra premium, therefore, might well fit the statistics. The duration table suggests that one cannot expect much change in the mortality by duration and that reductions in rating (one of the underwriter's troubles) are not to be encouraged. On the other hand, as the text mentions, the diagnosis and treatment of ulcers has improved, and this high mortality continued into the later durations may arise from the type of operation in vogue ten and more years ago. Subtotal gastrectomy, now perhaps the more common type of operation, may give better results, and there may be in this impairment, extra mortality decreasing with duration.

The next group, G 2, *"Carcinoma with operation once within 6 - 10 years of application", is of great underwriting interest.*

TABLE 8

G 2 — Carcinoma with operation once within 6 - 10 years of application

Age at issue	Actual deaths	Mortality ratio	Duration	Actual deaths	Mortality ratio
15 - 29	0	0	1 - 2	1	54
30 - 39	3	240	3 - 5	11	335
40 - 49	7	238	6 - 10	8	188
50 - 64	12	169	11 - 15	2	100
15 - 64	22	193	1 - 15	22	193

The impairment presents many problems in an attempt to find a rating from the figures. One-third of the experience was on female lives which meant that the expected mortality is to some

extent understated, and the mortality ratio is too low. All the excess deaths came from malignant neoplasms. The experience is very limited, but it suggests a decreasing mortality to be compensated for by a temporary extra premium. In analyzing the figures for possible ratings it is possible to take advantage of statistical concepts — in this instance the confidence interval. The Mortality Ratios at durations 3 - 5 and 6 - 10 become $335\ ^{+94}_{-72}$ and $188\ ^{+66}_{-47}$, respectively. Taking the upper (pessimistic) limit and translating it into extra deaths per thousand gives the following.

G 2

Duration	Adjusted deaths	Extra deaths per M
3 - 5	14	17.6
6 - 10	11	13.9

These figures are net — any extra premium based on them would have to be loaded — a matter for the actuary. The conservative approach, however, indicates that the net temporary extra must be at least $18 per $1,000.

These illustrations from one or two impairments have shown some of the difficulties in this problem of finding the ratings. There are others equally difficult, such as the impairment where the mortality ratio is just below or just above 125 per cent. For example. A 40, *"Acute articular rheumatism, one attack, within 5 years of application"*:

TABLE 9

A 40 — Acute articular rheumatism, one attack, within 5 years of application

Age at issue	Mortality ratio	
	Standard	Substandard
15 - 29	182	162
30 - 39	127	130
40 - 49	92	51
50 - 64	142	137
All	129	121

Duration	Extra Deaths per M	
	Standard	Substandard
1 - 2	1.01	—0.34
3 - 5	0.87	0.94
6 - 10	1.18	—0.40
11 - 15	—0.47	4.14
1 - 15	0.84	0.44

The patterns are similar for both standard and substandard. Does this mean that it is necessary to rate the lives under 30 more severely? The extra deaths are practically one per thousand by duration in the standard group while the bulk of the extra deaths come at duration 11 - 15 in the substandard group. The causes of death in both groups are interesting. Neither group shows a high ratio for heart and circulatory diseases. The standard group has 27 deaths (policies) from accident, homicide and suicide (expected 15.7) and the total number of extra deaths in the group is 24. If deaths from these causes are distributed throughout the tables on the same basis as all extra deaths then the experience is obviously within the standard range. This could be checked only by a very detailed study of the basic figures.

Outside of the statistical limitations, and the limitations inherent in the heterogeneous nature of the data, there is one problem that has as yet no satisfactory answer, and that is the effect of the secular trend of mortality upon impaired lives. There are two forces at work on improving mortality. One is the improvement in medical and surgical technics in dealing with disease; the other is the generally improving health of the entire population, aided and abetted by the medical profession in its many aspects. Table 10 (which is table 1 divided by lines corresponding to the various periods) illustrates the problem.

TABLE 10

Year of Issue	1936	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946
1935	1	2	3	4	5	6	7	8	9	10	11
1936		1	2	3	4	5	6	7	8	9	10
1937			1	2	3	4	5	6	7	8	9
1938				1	2	3	4	5	6	7	8
1939					1	2	3	4	5	6	7
1940						1	2	3	4	5	6
1941							1	2	3	4	5
1942								1	2	3	4
1943									1	2	3
1944										1	2
1945											1

The experience of durations 1 and 2, for example, passes through a series of years 1936-1939, 1940-1943, 1944-1946, during which

mortality has been definitely improving. We do not know what the basic mortality is in each of these groups of years, and the Basic Table is a compound of 15 years. The Basic Tables in the Study provide us with a numerical illustration. For the Study two Basic Tables were constructed, 1935-1950 and 1946-1950. A comparison of the mortality rates for the first two policy years shows that the rates for the later table are 80 per cent of the earlier table, and since the earlier table contains the later, the mortality rates 1935-1945 must be considerably higher than those of the entire table. Depending, therefore, on where the deaths fall it is possible to have understated or overstated the expected deaths. The mortality ratio, in any event, is a compound affair, made up of various generation tables, corresponding to the years of issue.

The nature of the problem can be shown in oversimple terms by referring to A 7, to that portion of the experience covering durations 1 - 2.

Duration	Exposed	Actual deaths	Expected deaths	Mortality ratio
1 -2	33406	123	51.93	237

If all the deaths occurred in the issues of 1946 - 1950 (which probably did not happen) the expected deaths should be 80 per cent of those given in the table and the mortality ratio increases from 237 per cent to 300 per cent.

The Study mentions that the death rate in substandard impairments has decreased even though the actual to expected mortality ratio has remained constant, or even increased. Not enough detailed information is available to make a comparison of the absolute rates on any impairment with those of the previous studies and because of the small numbers the comparison might not mean much. If we had the absolute rate of mortality on gastric ulcer, that is, by age and duration for the 1929 and 1951 Studies it could be estimated whether the substandard ratios to standard were remaining constant, or possibly diverging from the standard trend. As long as the basic mortality is not improving too rapidly the substandard ratios can be taken as guides to the future; if the basic mortality is improving, as it has been, very rapidly, then the ratios have to be used with greater caution.

This is the statistical side, but there is another, the medical side, and since the underwriter is trying to approximate future mortality, he has to consider both the statistical and medical aspects. The Study mentions that the results do not provide a highly reliable guide to future experience because of the continuing advance in medical sciences and public health. It is in this area of changing underwriting concepts that the medical officers of the companies have had, and should continue to have, great influence. Here the clinical concept is important and the clinical concept may induce the underwriter to take a more optimistic or a more pessimistic view than the statistics would seem to justify. The important point is that everyone should be constantly aware of the changing front in all branches of medicine when trying to translate the results of an impairment study into ratings for future use.

This point was mentioned in connection with ulcers, a group in which there may be expected more accurate diagnosis and possibly more successful treatment in the future. A set of ratings with this in view could give better results than the Study alone would justify. This would, however, put a burden on the underwriter to see that he gets complete information for classification purposes if he is to use the more favorable ratings.

Underwriting is like medicine, a science and an art. The statistics provide a certain scientific background, the medical director provides needed help in the art of appraising all factors that go to make up a risk.

Finally, a note of caution may not be out of place. This is not the last study to be seen and maybe more problems arise from overweight and blood pressure than from the many other impairments that have been so recently investigated. The next report on Weight and Blood Pressure will possibly yield more food for thought and more rating problems to solve.

The author's thanks are due to Mr. Neil Macintyre and Mr. W. H. Schmidt of the Mutual Life Insurance Company of New York for helpful criticisms and suggestions.

DR. HARRY E. UNGERLEIDER — I would like to say one thing here, that every time a medical impairment study is made we hear the same complaint, that the material is heterogeneous and that the criteria for the study are made at the time the study is made.

It seems to me, Mr. President, that we ought to give considera-

tion, in any future studies, to laying the protocol, the experiment, now, and have understandings as to what each category is. For example, the one that was cited, on acute articular rheumatism, was definitely a "hodgepodge" and meant nothing.

I think we should have some real study of the various entities and set them up in really defined compartments, so that when a statistical study is made, we can obviate, as much as possible, ever-recurring accusations of heterogeneity, which vitiates most of the study.

MR. WEBSTER — I have a great deal of sympathy with Dr. Ungerleider on this. On the other hand, I go back to the point I made, that we are running a business and not a research laboratory. Our job is to issue insurance to as large a number of the people of these United States and Canada as are willing to put up the money to pay for it.

I would like to see some lines laid down on certain impairments. One of your members suggested, in one of the previous discussions of this Study, that some work might be done on the urinalysis group of impairments because of the obvious lack of any standards. I think that is something that might be followed up.

I am not complaining about the heterogeneous nature of the statistics. I am trying to point out that when you are interpreting them, you must remember that they are heterogeneous and not be misled, and, certainly, do not be misled by percentages.

Most of you know the story about the nonprohibitionist orator who was extolling the virtues of temperance. He pointed out that in a certain regiment during the war, 50 per cent of the teetotallers were killed and only 5 per cent of the drinkers. He did not say that there were only two teetotallers in the regiment.

PRESIDENT WILLIS — Thank you, Mr. Webster, for your very enlightening talk. We are more than glad to have your opinion on this subject and your talk was most pleasing.

We have now come to the end of our scientific program. To those of you who have not met them, I would like to introduce your future officers: President-elect Dr. Edson E. Getman, Medical Director of the New York Life.

The new Vice-President is Dr. Norman Barker, Medical Director of Connecticut General Life Insurance Company. He is unfortunately not present.

As you know, the other officers — Dr. Grant Irving, Treasurer; Dr. Henry B. Kirkland, Secretary; and Dr. James Gudger, Editor of the *Proceedings* — were reelected to these positions.

I wish to thank all the guest speakers for the splendid papers they have presented and the time they have given us. I also wish to thank the officers and the chairmen and the members of all our committees for the fine work they have done and the help they have been to me. I am especially grateful to Dr. Albert Pollack of my own staff for his advice and assistance in preparing this program.

I wish to express my deep appreciation to Dr. Henry B. Kirkland for his guidance and advice throughout the past year. I would have floundered many times without his help.

And then, my sincere thanks to Miss Clara Rizzolo, who has been secretary to Secretaries of this Association for so many years that she must have started in early childhood. Past presidents know, and future presidents will learn, that she knows all the answers.

I also wish to thank Miss Wickman and my own secretary, Miss O'Brien, for seeing that this meeting ran smoothly.

The time has now come for me to turn this meeting over to your new President. It has been my pleasure to know him intimately, and I have leaned on him heavily. The Association is fortunate in having Dr. Ralph R. Simmons, Medical Director of the Equitable Life Insurance Company of Iowa, as our president for the next year. Please come forward, Dr. Simmons.

PRESIDENT SIMMONS — Fellow Members of the Association and Guests: It is with a feeling of deepest gratitude and humility that I enter upon my duties as president of this fine body. I am further keenly appreciative of the challenge in maintaining the high standards of professional excellence established in the program to which we have listened during the past three days. It is, indeed, difficult to follow in the presidency of the Association such men as Dr. Willis, Dr. Montgomery, Dr. Bonnett and the others who have so ably served in this office during previous years. With your help, however, I hope that we can have another good and profitable meeting next October.

At this time, I would like to tell you a little about our plans for the meeting of 1956. Barring the displeasure of the Executive Committee at their next annual session, which might and could reverse my decision — in which case I shall be somewhere in China in 1956 — the meeting will be held at New Orleans next year. The dates will be Tuesday, Wednesday, Thursday and possibly Friday, if we have a special program on accident and sickness insurance, October 23, 24, 25 and possibly 26. Believing that this time and place will prove highly attractive, not only for a successful scientific meeting but also as a pleasing locale for an outing for you and your family, we plan from time to time to advise you of the attractions of New Orleans and its environs during the October season. Some of you may wish to plan your vacations around this meeting, and we hope to be able to give you information to this end.

I would add that plans are being made for the entertainment of the ladies and the children, so plan to come to New Orleans on October 23 through 25, 1956, and bring the entire family with you.

Is there any further business to come before the Association? I recognize Dr. Bonnett.

Dr. Earl C. Bonnett — Mr. Chairman and Fellow Members: Dr. Willis has already thanked all of those who contributed so much to this very excellent program. I would like to take this opportunity to move a resolution of thanks and appreciation to Dr. Willis, to acknowledge our indebtedness for this very excellent program. He arranged it and carried it out, with the help of others, but with a great deal of work, I know from experience, that he did himself. In addition to arranging the program, he carried it through with dispatch and promptness.

President Simmons — While Dr. Bonnett made that in the form of a motion, I am sure your applause is recognition of the unanimous feeling of this body, of our indebtedness to you, Dr. Willis.

Is there any further business to come before the Association? If not, I now declare the Sixty-fourth Annual Meeting of this Association adjourned.

The following doctors were present at some time during the sessions:

F. B. Agee, Jr.
C. B. Ahlefeld
Joseph Altman
F. R. Anderson
K. W. Anderson
G. B. Appleford

Bernard Baillargeon
N. J. Barker
G. P. Barnett
S. F. Bassett
C. C. Beach
E. F. Beach
J. R. Beard
M. F. Bell
M. B. Bender
D. M. Benford
C. C. Berwick
W. R. Bishop
Abraham Block
H. L. Bockus
J. E. Boland
William Bolt
E. C. Bonnett
M. T. Boss
E. L. Boylen
W. R. Bradley
K. F. Brandon
D. J. Breithaupt
H. J. Brekke
E. J. Brogan
M. P. Brolsma
A. W. Bromer
C. H. Brown
H. B. Brown
R. F. Buchan
J. H. Burchenal

D. B. Campbell
R. L. Candage
P. H. Charlton
H. E. Christensen
R. B. Cleveland
M. H. Clifford
N.B.Cole
H. L. Colombo
B. R. Comeau
F. R. Congdon
C. E. Cook
J. L. Cook
M. J. Crilly

B. A. Dawber
H. D. Delamere
Aniceto Del Rio
W. S. Dietrich
F. R. Dieuaide
E. S. Dillon
J. A. Dillon
H. W. Dingman
William Dock
A. H. Domm
R. M. Donauer
J. P. Donelan
G. D. Dorman

L. H. Earle, Jr.
T. M. Ebers
L. J. Emanuele
J. A. End
Paul Entmacher

A. H. Faber
D. R. Faringer, Jr.
R. K. Farnham
H. H. Fellows
R. M. Filson
R. W. Finegan

F. I. Ganot
I. K. Gardner
D. S. Garner
J. H. Geddes
J. T. Geiger
W. M. Genthler
E. E. Getman
C. A. Gianasi
R. A. Goodell
George Goodkin
H. M. Goodman
H. W. Goos
J. K. Gordon
R. S. Gordon
C. D. Gossage
A. S. Graham
G. M. Graham
R. S. Graham
A. E. Gras
R. S. Gubner
J. R. Gudger
V. W. Gunter
F. R. N. Gurd

Llewellyn Hall
F. T. Hallam
G. W. Halpenny
V. G. Hammond
O. E. Hanes
F. M. Hanger
J. A. A. Harcourt
O. C. Hardwig
F. F. Harris
H. L. Hauge
W. C. Hausheer
H. M. Hawkins
J. G. Heard
M. H. Henderson
O. C. Hendrix
E. V. Higgins
W. H. Hill
E. C. Hillman, Jr.
E. A. Hines, Jr.
D. W. Hoare
C. F. Hofrichter
D. V. Holman
J. C. Horan
E. G. Howe
T. B. Hoxie
A. A. Humphrey
J. H. Humphries
B. J. Huntington
J. J. Hutchinson
J. R. B. Hutchinson
G. B. Hutchison

A. S. Irving
J. G. Irving

A. N. Jay
J. W. Johnson, Jr.
R. M. Johnson
Nathaniel Jones

V. L. Karren
E. A. Keenleyside
E. F. Kerby
N. C. Kiefer
C. E. Kiessling
D. G. Kilgore
Richard King
C. T. Kirchmaier
H. B. Kirkland
W. L. Knott
Edward Kuck

Phillips Lambkin
P. H. Langner, Jr.
L. G. La Pointe
W. F. Larrabee, Jr.
A. L. Larson
H. R. Leffingwell
J. S. Lentz

C. P. LeRoyer, Jr.
W. R. Leute, Jr.
S. A. Levine
E. H. Lindstrom
G. W. Lougheed
G. J. Lunz

F. M. McChesney
H. M. McCue, Jr.
William MacDonald
A. J. McGanity
J. D. McGaughey, III
F. J. McGurl
T. J. McGurl, Jr.
George McLean
L. L. McLellan
W. J. McNamara
J. K. McShane
H. R. Magee
Morton Magiday
S. J. N. Magwood
John Malgieri
P. V. Martin
F. A. L. Mathewson
P. S. Metzger
M. B. Miller
Eugene Montgomery
R. C. Montgomery
J. F. Moore, Jr.
S. R. Moore
C. V. Mulligan
J. R. Murphy

S. A. Narins
R. M. Nay
M. H. Neill
R. A. Nelson
R. E. Nicholson

A. J. Oberlander
R. J. Oehrig
D. J. O'Leary
W. F. H. O'Neill
J. K. T. Ormrod

A. E. Parks
J. S. Pearson
D. S. Pepper
R. W. Peterson
J. C. Pierson
Cullen Pitt
T. E. Plucinski
G. J. Pohly
A. A. Pollack
Herbert Pollack
L. S. Powell
W. O. Purdy
R. S. A. Purkis
M. A. Puzak

R. R. Rambo
J. H. Ready
C. L. Reeder
P. V. Reinartz
W. M. Reynolds
H. G. Riche
G. P. Robb
D. C. Roberts
J. C. Robinson
H. B. Rollins
R. C. Roskelley
J. G. Ross
T. F. Ross
E. F. Russell
N. E. Ruud
M. T. Ryman

R. S. Schaaf
K. F. Schaefer
L. P. Schroeder
P. C. Schwager
B. T. D. Schwarz
W. H. Scoins
R. C. Secor
A. F. Seibert
D. L. Selby
J. T. Sheridan
R. R. Simmons
G. A. Simpson
R. B. Singer

B. W. Sitterson
W. A. Smith
W. H. Spittel
C. G. Spivey
F. L. Springer
H. F. Starr
H. F. Starr, Jr.
D. F. R. Steuart
E. M. Stevenson
F. M. Stites

J. L. Tansey
M. J. Taylor
L. J. Tedesco
G. F. Tegtmeyer
W. B. Thornton
Joseph Travenick, Jr.
Wallace Troup
F. D. Truax

H. E. Ungerleider

R. C. Voss

P. C. Waldo
K. K. Wallace
K. E. Ward
R. V. Ward
F. A. Warner
G. H. Watters
Jefferson Weed
J. L. Weinstock
S. S. Werth
J. A. Wilhelm
E. S. Williams
R. L. Willis
A. C. Wilson
J. S. Winder
D. H. Woodhouse

L. S. Ylvisaker
D. E. Yochem
G. G. Young

R. W. Zinkann
A. F. Zipf

Also present were:

J. F. Anderson
C. H. Edwards
Arthur Hunter
Edward King
Earl MacRae
W. A. Merriam
A. P. Morton

Pearce Shepherd
O. G. Sherman
W. M. Stufflebeem

Paul Thomson
A. E. Thyselius

R. J. Vanderbeck

Robert Walker
A. C. Webster
Earl Weltz
Sidney Whipple
J. C. Wilberding
Arthur Windecker

Miss A. M. Lyle
Miss Hazel Wallace

Total attendance at all sessions, 296.

In Memoriam

Deceased since the Sixty-third Annual Meeting

William W. Rucks, M. D.
Home State Life Insurance Company,
Oklahoma City, Okla.
Died July 14, 1955

William H. Ward, M. D.
The Mutual Benefit Life Insurance Company,
Newark, N. J.
Died February 10, 1955

LIST OF MEMBERS OF THE ASSOCIATION OF LIFE INSURANCE MEDICAL DIRECTORS OF AMERICA

Fred B. Agee, Jr., M. D.	Aetna, Hartford, Conn.
Charles B. Ahlefeld, M. D.	Business Men's, Kansas City, Mo.
Arthur C. Albright, M. D.	Victory Mutual, Chicago, Ill.
Henry Almond, M. D.	Metropolitan, New York City
Joseph Altman, M. D.	Companion Life, New York City
E. A. Anderson, M. D.	Modern Woodmen, Rock Island, Ill.
Frank R. Anderson, M. D.	Pacific Mutual, Los Angeles, Calif.
Karl W. Anderson, M. D.	Northwestern National, Minneapolis, Minn.
Perry A. Anderson, M. D.	Rockford Life, Rockford, Ill.
George B. Appleford, M. D.	Berkshire, Pittsfield, Mass.
Thomas M. Armstrong, M. D.	Philadelphia Life, Philadelphia, Pa.
William B. Aten, M. D.	Security Mutual, Binghamton, N. Y.
Bernard Baillargeon, M. D.	Alliance Nationale, Montreal, Canada
Norman J. Barker, M. D.	Connecticut General, Hartford, Conn.
Gordon P. Barnett, M. D.	Kansas City Life, Kansas City, Mo.
Charles M. Barrett, M. D.	Western and Southern, Cincinnati, Ohio
Samuel F. Bassett, M. D.	Prudential, Newark, N. J.
Daniel S. Baughman, M. D.	Security Life and Accident, Denver, Colo.

Eliot F. Beach, Ph. D.	Metropolitan, New York City
J. Randolph Beard, M. D.	Mutual Benefit, Newark, N. J.
James E. Bee, M. D.	Kansas City Life, Kansas City, Mo.
Murray F. Bell, M. D.	New York Life, New York City
Maurice B. Bender, M. D.	Guardian, New York City
David M. Benford, M. D.	Metropolitan, New York City
Robert A. Benson, M. D.	Metropolitan, Ottawa, Canada
Roy W. Benton, M. D.	Northwestern Mutual, Milwaukee, Wis.
C. Coleman Berwick, M. D.	Metropolitan, San Francisco, Calif.
Francis P. Bicknell, M. D.	State Mutual, Worcester, Mass.
B. Cosby Bird, M. D.	Preferred, Montgomery, Ala.
William R. Bishop, M. D.	Provident Life Acc., Chattanooga, Tenn.
Abraham Block, M. D.	Workmen's Benefit, Brooklyn, N. Y.
John E. Boland, M. D.	Country, Chicago, Ill.
William Bolt, M. D.	New York Life, New York City
John M. Bond, M. D.	Northwestern Mutual, Milwaukee, Wis.
Earl C. Bonnett, M. D.	Metropolitan, New York City
M. Theodore Boss, M. D.	Home Friendly, Baltimore, Md.
John R. Bowen, M. D.	Penn Mutual, Philadelphia, Pa.
J. Thornley Bowman, M. D.	London Life, London, Canada
Ernest L. Boylen, M. D.	Standard, Portland, Ore.
Robert D. Boynton, M. D.	State Mutual, Worcester, Mass.
William R. Bradley, M. D.	Phoenix Mutual, Hartford, Conn.

William E. Branch, M. D.	Constitution Life, Los Angeles, Calif.
Kenneth F. Brandon, M. D.	Aetna, Hartford, Conn.
David J. Breithaupt, M. D.	Manufacturers, Toronto, Canada
Harvey J. Brekke, M. D.	Lutheran Brotherhood, Minneapolis, Minn.
Robert D. Brewer, Jr., M. D.	Prudential, Chicago, Ill.
Edmund J. Brogan, M. D.	Provident Mutual, Philadelphia, Pa.
Albert W. Bromer, M. D.	Metropolitan, New York City
C. Frank Brown, M. D.	Southwestern, Dallas, Tex.
Frederick R. Brown, M. D.	New England Mutual, Boston, Mass.
Howard B. Brown, M. D.	Massachusetts Mutual, Springfield, Mass.
Ronald F. Buchan, M. D.	Prudential, Newark, N. J.
Carroll A. Burroughs, M. D.	Peoples, Frankfort, Ind.
Benjamin F. Byrd, M. D.	National Life & Accident, Nashville, Tenn.
W. Lawrence Cahall, Jr., M. D.	John Hancock Mutual, Boston, Mass.
Douglas B. Campbell, M. D.	National, Toronto, Can.
W. Allan Campbell, M. D.	Bankers, Lincoln, Neb.
Raymond L. Candage, M. D.	State Mutual, Worcester, Mass.
David W. Carter, Jr., M. D.	Reserve Life, Dallas, Tex.
Paul H. Charlton, M. D.	Midland Mutual, Columbus, Ohio
Edmund D. Chesebro, M. D.	Puritan, Providence, R. I.
Harry E. Christensen, M. D.	Union Mutual, Portland, Me.
Norman S. Clark, M. D.	Independent Order of Foresters, Toronto, Can.

Howard R. Clement, M. D.	John Hancock Mutual, Boston, Mass.
Robert B. Cleveland, M. D.	Equitable Life Assurance, New York City
Milton H. Clifford, M. D.	New England Mutual, Boston, Mass.
Harry A. Cochran, Jr., M. D.	Lincoln National, Fort Wayne, Ind.
John E. C. Cole, M. D.	North American, Toronto, Canada
Norman B. Cole, M. D.	Baltimore Life, Baltimore, Md.
Irwin E. Colgin, M. D.	Texas Life, Waco, Tex.
G. R. Collyer, M. D.	London Life, London, Canada
Harry L. Colombo, M. D.	National Life, Montpelier, Vt.
Frederick R. Congdon, M. D.	Berkshire, Pittsfield, Mass.
Chester E. Cook, M. D.	Southwestern, Dallas, Tex.
J. Lindsay Cook, M. D.	Pilot, Greensboro, N. C.
Robert H. Craig, M. D.	Mutual, Waterloo, Can.
Marc J. Crilly, M. D.	Equitable Life Assurance, New York City
Neil L. Criss, M. D.	United Benefit, Omaha, Neb.
Henry A. Cromwell, M. D.	American Capitol, Houston, Tex.
Howard K. Crutcher, M. D.	United Fidelity, Dallas, Tex.
Khurshed J. J. Cursetji, M. D.	Oriental Government Security Life, Bombay, India
Cornelius C. Davis, M. D.	Prudential, Houston, Tex.
Bryan A. Dawber, M. D.	Penn Mutual, Philadelphia, Pa.
John S. Delahaye, M. D.	Empire Life, Kingston, Canada
Harold D. Delamere, M. D.	Crown, Toronto, Canada

Aniceto Del Rio, M. D.	La Nacional, Mexico City, Mexico
Earle T. Dewey, M. D.	Metropolitan, San Francisco, Calif.
Walter S. Dietrich, M. D.	Metropolitan, New York City
Harry W. Dingman, M. D.	Continental Assurance, Chicago, Ill.
Albert H. Domm, M. D.	Prudential, Los Angeles, Calif.
Robert M. Donauer, M. D.	Prudential, Newark, N. J.
James P. Donelan, M. D.	Guarantee Mutual, Omaha, Neb.
Verner J. Donnelly, M. D.	Prudential, Houston, Tex.
Gerald D. Dorman, M. D.	New York Life, New York City
James T. Downs, Jr., M. D.	Fidelity Union, Dallas, Tex.
Raymond L. Dross, M. D.	Prudential, Houston, Tex.
Thomas C. Dunlop, M. D.	Manufacturers, Toronto, Canada
Louis B. Dunn, M. D.	Postal, New York City
William W. Eakin, M. D.	Standard, Montreal, Canada
Lyon H. Earle, Jr., M. D.	Connecticut General, Hartford, Conn.
Theodore M. Ebers, M. D.	Connecticut Mutual, Hartford, Conn.
H. Glenn Ebersole, M. D.	Central Standard, Monmouth, Ill.
Laurence B. Ellis, M. D.	Boston Mutual, Boston, Mass.
Louis J. Emanuele, M. D.	New York Life, New York City
James C. Emmett, M. D.	Imperial, Toronto, Canada
Jack A. End, M. D.	Northwestern Mutual, Milwaukee, Wis.

Albert H. Faber, M. D.	New York Life, New York City
J. Gilbert Falconer, M. D.	North American, Toronto, Canada
Raymond K. Farnham, M. D.	Metropolitan, New York City
Haynes H. Fellows, M. D.	Metropolitan, New York City
William S. Fewell, M. D.	Liberty, Greenville, S. C.
Ralph M. Filson, M. D.	Travelers, Hartford, Conn.
Rexford W. Finegan, M. D.	Metropolitan, New York City
James G. Forgerson, M. D.	Metropolitan, San Francisco, Calif.
Philip M. L. Forsberg, M. D.	United Life and Accident, Concord, N. H.
Garth E. Fort, M. D.	National Life & Accident, Nashville, Tenn.
Arthur C. Fortney, M. D.	Western States, Fargo, N. D.
John M. Foster, M. D.	Capitol, Denver, Colo.
John T. France, M. D.	State Farm, Bloomington, Ill.
Edward M. Freeland, M. D.	New York Life, New York City
Clarence E. Fronk, M. D.	Hawaiian Life, Honolulu, T. H.
Robert E. Funke, M. D.	Prudential, Los Angeles, Calif.
F. Irving Ganot, M. D.	Prudential, Newark, N. J.
I. Kenneth Gardner, M. D.	Lincoln National, Ft. Wayne, Ind.
David S. Garner, M. D.	Shenandoah, Roanoke, Va.
J. H. Geddes, M. D.	Northern, London, Canada
John T. Geiger, M. D.	Metropolitan, New York City
John P. Gemmell, M. D.	Monarch, Winnipeg, Canada

William M. Genthner, M. D.	Continental American, Wilmington, Del.
Edson E. Getman, M. D.	New York Life, New York City
Charles A. Gianasi, M. D.	Continental Assurance, Chicago, Ill.
Edgar G. Givhan, Jr., M. D.	Protective, Birmingham, Ala.
Robert A. Goodell, M. D.	Phoenix Mutual, Hartford, Conn.
George Goodkin, M. D.	Equitable Life Assurance, New York City
Harold M. Goodman, M. D.	Home Beneficial, Richmond, Va.
Harry W. Goos, M. D.	Home, Philadelphia, Pa.
J. Keith Gordon, M. D.	Sun, Montreal, Canada
Charles D. Gossage, M. D.	Confederation, Toronto, Canada
Angus S. Graham, M. D.	London Life, London, Canada
George M. Graham, M. D.	Lincoln National, Fort Wayne, Ind.
Robert S. Graham, M. D.	Equitable Life Assurance, New York City
Albert E. Gras, M. D.	Prudential, Newark, N. J.
Ghent Graves, M. D.	American General, Houston, Tex.
Harris M. Gray, M. D.	Manufacturers, Toronto, Canada
Floyd M. Green, M. D.	Columbus Mutual, Columbus, Ohio
George E. Greenway, M. D.	Western Life Assurance, Hamilton, Canada
C. J. M. Grisdale, M. D.	Continental Assurance, Chicago, Ill.
Frederick O. Gronvold, M. D.	Pioneer Mutual, Fargo, N. D.
Bruce F. Grotts, M. D.	Prudential, Chicago, Ill.
Richard S. Gubner, M. D.	Equitable Life Assurance, New York City
James R. Gudger, M. D.	Mutual, New York City

Van W. Gunter, M. D.	Jefferson Standard, Greensboro, N. C.
Frank R. N. Gurd, Ph. D.	Equitable Life Assurance, New York City
Milton W. Gwinner, M. D.	Western and Southern, Cincinnati, Ohio
Thomas R. Hale, M. D.	Sun, Montreal, Canada
Llewellyn Hall, M. D.	Phoenix Mutual, Hartford, Conn.
F. Tulley Hallam, M. D.	Bankers, Des Moines, Iowa
John H. Halliday, M. D.	Australian Mutual, Sydney Australia
Gerald W. Halpenny, M. D.	Royal, Montreal, Canada
Vincent G. Hammond, M. D.	Security Mutual, Binghamton, N. Y.
Ottis E. Hanes, M. D.	Life Ins. Co. of Ga., Atlanta, Ga.
John A. A. Harcourt, M. D.	Toronto Mutual, Toronto, Canada
Frank F. Harris, M. D.	Volunteer State, Chattanooga, Tenn.
T. Haynes Harvill, M. D.	Preferred Life, Dallas, Tex.
Garland M. Harwood, M. D.	Life Insurance Co. of Virginia, Richmond, Va.
Louis E. Hathaway, Jr., M. D.	Monarch, Springfield, Mass.
Howard L. Hauge, M. D.	New York Life, New York City
Walter C. Hausheer, M. D.	Prudential, Newark, N. J.
Harry M. Hawkins, M. D.	Old Line, Milwaukee, Wis.
Thomas L. Hawkins, M. D.	Western, Helena, Mont.
J. Harry Hayes, M. D.	Union, Little Rock, Ark.
Harvey D. Hebb, M. D.	Life Insurance Co. of Alberta Edmonton, Canada

Milton H. Henderson, M. D.	Excelsior, Toronto, Canada
Olin C. Hendrix, M. D.	New England Mutual, Boston, Mass.
William A. Henry, M. D.	Franklin, Springfield, Ill.
Ivan C. Heron, M. D.	West Coast, San Francisco, Calif.
William D. Hickerson, M. D.	Union Central, Cincinnati, Ohio
Eugene V. Higgins, M. D.	North American Reassurance, New York City
Ernest C. Hillman, Jr., M. D.	Mutual Benefit, Newark, N. J.
Daniel W. Hoare, M. D.	Penn Mutual, Philadelphia, Pa.
Joseph C. Horan, M. D.	Metropolitan, New York City
Arnold B. Houston, M. D.	Great-West, Winnipeg, Canada
Edward G. Howe, M. D.	Prudential, Newark, N. J.
Thomas B. Hoxie, M. D.	New York Life, New York City
Henry W. Hudson, M. D.	Loyal Protective, Boston, Mass.
Gene I. Hull, M. D.	Bankers, Des Moines, Iowa
Merwin L. Hummel, M. D.	Acacia Mutual, Washington, D. C.
Arthur A. Humphrey, M. D.	Federal Life and Casualty, Battle Creek, Mich.
John L. Humphreys, M. D.	Lincoln National, Ft. Wayne, Ind.
James H. Humphries, M. D.	Home, New York City
J. Edward Hunsinger, M. D.	Republic Nat'l, Dallas, Tex.
Benjamin L. Huntington, M. D.	John Hancock Mutual, Boston, Mass.
Samuel W. Hurdle, M. D.	Security Life & Trust, Winston-Salem, N. C.
John J. Hutchinson, M. D.	New York Life, New York City

J. Raymond B. Hutchinson, M. D.	Acacia Mutual, Washington, D. C.
George B. Hutchison, M. D.	Equitable Life Assurance, New York City
Albert S. Irving, M. D.	Commonwealth, Louisville, Ky.
J. Grant Irving, M. D.	Aetna, Hartford, Conn.
Tsugitake Isshiki, M. D.	Asahi Mutual, Tokyo, Japan
Samuel Jagoda, M. D.	State Reserve, Fort Worth, Tex.
Hubert R. John, M. D.	Maccabees, Detroit, Mich.
Joseph W. Johnson, Jr., M. D.	Interstate Life and Accident, Chattanooga, Tenn.
Alfred Kahn, Jr., M. D.	National Equity, Little Rock, Ark.
Victor L. Karren, M. D.	Home, New York City
Edward A. Keenleyside, M. D.	Prudential, Toronto, Canada
Frank J. Kefferstan, II, M. D.	John Hancock Mutual, Boston, Mass.
Charles H. Kelley, M. D.	Columbian National, Boston, Mass.
Newell R. Kelley, M. D.	Bankers, Des Moines, Iowa
Herbert B. Kennedy, M. D.	Woodmen of the World, Omaha, Neb.
Roeinton B. Khambatta, M. D.	American Life, Karachi, Pakistan
Harry B. Kidd, M. D.	Metropolitan, Ottawa, Canada
Norvin C. Kiefer, M. D.	Equitable Life Assurance, New York City
Charles E. Kiessling, M. D.	Prudential, Newark, N. J.

Donald G. Kilgore, M. D.	Republic National, Dallas, Tex.
Richard King, M. D.	Family Fund, Atlanta, Ga.
Carl T. Kirchmaier, M. D.	Life & Casualty, Nashville, Tenn.
Henry B. Kirkland, M. D.	Prudential, Newark, N. J.
Norman L. Knott, M. D.	Prudential, Los Angeles, Calif.
Edward Kuck, M. D.	Union Central, Cincinnati, Ohio
Paul Kurzweg, Jr., M. D.	All American Assurance, Lafayette, La.
Ewart R. Lamb, M. D.	Paul Revere, Hamilton, Canada
Phillips Lambkin, M. D.	Guardian, New York City
Paul H. Langner, Jr., M. D.	Provident Mutual, Philadelphia, Pa.
L. Gordon LaPointe, M. D.	Manhattan Life, New York City
H. Franklyn Laramore, M. D.	Connecticut Mutual, Hartford, Conn.
Walter F. Larrabee, Jr., M. D.	Minnesota Mutual, St. Paul, Minn.
Albert L. Larson, M. D.	Travelers, Hartford, Conn.
Ivan C. Lawler, M. D.	New York Life, New York City
Linford H. Lee, M. D.	Pacific Mutual, Los Angeles, Calif.
James M. Leffel, M. D.	Empire L. & A., Indianapolis Ind.
Harold R. Leffingwell, M. D.	Paul Revere, Worcester, Mass.
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